

Serendipity Based Medicine (SBM) : To Infinity and Beyond

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I never did anything worth doing by accident, nor did any of my inventions come by accident; they came by work (Plato).

The more I draw and write, the more I realise that accidents are a necessary part of any creative act, much more so than logic or wisdom. Sometimes a mistake is the only way of arriving at an original concept, and the history of successful inventions is full of mishaps, serendipity and unintended results (Shaun Tan).

Necessity is the mother of invention.

Accident is the mother of invention.

Abstract

Serendipity means a "fortunate happenstance" or "pleasant surprise". Serendip is the Perso-Arab name for Sri Lanka (Ceylon).

How do we inspire new ideas that could lead to potential treatments for rare or neglected diseases, and allow for serendipity that could help to catalyze them?

How we can build a more concrete structure for the "idea-hypothesis testing-proof of concept-translation-breakthrough pathway" ?

What do Rollerblades, Häagen-Dazs ice cream, and Spider-Man movies have in common? The answer: Each is something that adults loved as children and that was reproduced in an expensive form for grown-ups. Asking brainstorming participants to ponder how their childhood passions could be recast as adult offerings might generate some fabulous ideas for new products or services.

Stories of serendipitous discoveries in medicine incorrectly imply that the path from an unexpected observation to major discovery is straightforward or guaranteed.

The causes of revolutionary science are varied and lack an obvious common structure. For many years, drug discovery was a target- and mechanism-agnostic approach that was based on ethnobotanical knowledge often fueled by serendipity.

There should be a greater appreciation for the importance of serendipity in scientific discovery. Serendipity Based Medicine (SBM) should be the present and future of medicine. Big Data will need Big Thinking.

Keywords : Serendipity, Medicine.

1. The Immortal Life of Henrietta Lacks

Henrietta Lacks (born Loretta Pleasant; August 1, 1920 – October 4, 1951) was an African American woman whose cancer cells were the source of the HeLa cell line, the first immortalized cell line and one of the most important cell lines in medical research. An immortalized cell line will reproduce indefinitely under specific conditions, and the HeLa cell line continues to be a source of invaluable medical data to the present day.

The Immortal Life of Henrietta Lacks (2010) is a nonfiction book by American author Rebecca Skloot (1).

Howard Wilbur Jones, Jr. (December 30, 1910 – July 31, 2015) was an American gynecological surgeon and in vitro fertilization (IVF) specialist.

Jones and his wife joined the faculty at Johns Hopkins on a part-time basis in 1948. He was the initial treating physician of Henrietta Lacks when she presented to Johns Hopkins with cancer in 1951. Jones took a biopsy of Lacks's tumor and, without her permission, sent samples to his laboratory colleagues. The cells, later known as HeLa cells, grew at an astonishing rate in the lab and were shipped and sold to researchers for various purposes. Research with the cells helped to facilitate medical breakthroughs, including the vaccines for polio and human papillomavirus, though controversy later arose because the cells were being used without the knowledge of Lacks or her family.

George Otto Gey (July 6, 1899 – November 8, 1970) was the cell biologist who propagated the HeLa cell line. Using a sample from

the cervix of Henrietta Lacks provided by Howard W. Jones, he propagated her cells into an immortalized human cell line.

2. Serendipity

Serendipity means a "fortunate happenstance" or "pleasant surprise". The term was coined by Horace Walpole in 1754. In a letter he wrote to a friend, Walpole explained an unexpected discovery he had made by reference to a Persian fairy tale, *The Three Princes of Serendip*. The princes, he told his correspondent, were "always making discoveries, by accidents and sagacity, of things which they were not in quest of".

The notion of serendipity is a common occurrence throughout the history of scientific innovation. Examples are Alexander Fleming's accidental discovery of penicillin in 1928, the invention of the microwave oven by Percy Spencer in 1945, and the invention of the Post-it note by Spencer Silver in 1968.

In June 2004, a British translation company voted the word to be one of the ten English words hardest to translate. However, due to its sociological use, the word has since been exported into many other languages.

3. The Three Princes of Serendip

The Three Princes of Serendip is the English version of the story *Peregrinaggio di tre giovani figliuoli del re di Serendippo* published by Michele Tramezzino in Venice in 1557. Tramezzino claimed to have heard the story from one Christopher Armeno, who had translated the Persian fairy tale into Italian, adapting Book One of Amir Khusrau's *Hasht-Bihisht* of 1302. The story first came to English via a French translation, and now exists in several out-of-print translations. Serendip is the Perso-Arabic name for Sri Lanka (Ceylon).

The story has become known in the English-speaking world as the source of the word serendipity, coined by Horace Walpole because of his recollection of the part of the "silly fairy tale" in which the three princes by "accidents and sagacity" discern the nature of a lost camel. In a separate line of descent, the story was used by Voltaire in his 1747 *Zadig*, and through this contributed to both the evolution of detective fiction and the self-understanding of scientific method.

4. Enabling Anyone to Translate Clinically Relevant Ideas to Therapies

How do we inspire new ideas that could lead to potential treatments for rare or neglected diseases, and allow for serendipity that could help to catalyze them? How many potentially good ideas are lost because they are never tested? What if those ideas could have led to new therapeutic approaches and major healthcare advances? If a clinician or anyone for that matter, has a new idea they want to test to develop a molecule or therapeutic that they

could translate to the clinic, how would they do it without a laboratory or funding? These are not idle theoretical questions but addressing them could have potentially huge economic implications for nations. If we fail to capture the diversity of ideas and test them we may also lose out on the next blockbuster treatments. Many of those involved in the process of ideation may be discouraged and simply not know where to go. We try to address these questions and describe how there are options to raising funding, how even small scale investments can foster preclinical or clinical translation, and how there are several approaches to outsourcing the experiments, whether to collaborators or commercial enterprises. While these are not new or far from complete solutions, they are first steps that can be taken by virtually anyone while we work on other solutions to build a more concrete structure for the "idea-hypothesis testing-proof of concept-translation-breakthrough pathway" (2).

5. Breakthrough thinking from inside the box

Companies often begin their search for great ideas either by encouraging wild, outside-the-box thinking or by conducting quantitative analysis of existing market and financial data and customer opinions. Those approaches can produce middling ideas at best, say Coyne, founder of an executive-counseling firm in Atlanta, and Clifford and Dye, strategy experts at McKinsey. The problem with the first method is that few people are very good at unstructured, abstract brainstorming. The problems with the second are that databases are usually compiled to describe current--not future--offerings, and customers rarely can tell you whether they need or want a product if they've never seen it. The secret to getting your organization to regularly generate lots of good ideas, and occasionally some great ones, is deceptively simple: First, create new boxes for people to think within so that they don't get lost in the cosmos and they have a basis for offering ideas and knowing whether they're making progress in the brainstorming session. Second, redesign ideation processes to remove obstacles that interfere with the flow of ideas--such as most people's aversion to speaking in groups larger than ten. This article offers a tested approach that poses concrete questions. For example, what do Rollerblades, Häagen-Dazs ice cream, and Spider-Man movies have in common? The answer: Each is something that adults loved as children and that was reproduced in an expensive form for grown-ups. Asking brainstorming participants to ponder how their childhood passions could be

recast as adult offerings might generate some fabulous ideas for new products or services (3).

6. Methylene Blue: The Long and Winding Road from Stain to Brain: Part 1.

Methylene blue, first discovered and used as a dye in the textile industry, has long been used for biological staining in histology, bacteriology, and hematology. Because of its unique physiochemical properties, it was the first synthetic drug used in medicine, having been used to treat malaria more than one century ago. Methylene blue was also one of the first drugs used for the treatment of patients with psychosis at the end of the 19th century and was the lead drug in the serendipitous development of phenothiazine antipsychotic drugs in the mid-20th century. It was studied in bipolar disorder in the 1980s and has been investigated in neurodegenerative disorders in recent years. The history of methylene blue from its discovery as a dye to its use as a stain and then its therapeutic application in medicine is an example of how a drug's use can evolve over time through careful observation, clinical needs, serendipity, and the integration of concepts from different disciplines (4).

7. Creativity needs some serendipity: Reflections on a career in ingestive behavior.

"I describe my 50 year career in ingestive behavior in the hope of inspiring young scientists to join in the excitement of discovering why animals, especially the human animal, eat and drink. My interest in ingestive behavior started by chance in a freshman biology class at the University of Pennsylvania taught by Alan Epstein. Once I was exposed to the thrill of doing research my plans for medical school were abandoned and I traveled to the University of Cambridge in England where with James Fitzsimons I completed a Ph.D. in physiology on studies of thirst in rats. After I moved on to the University of Oxford, the early training in biologic mechanisms provided a good basis for studies in humans. We characterized the sensations associated with thirst and the mechanisms involved in its initiation and termination. We also continued to work with animal models in a series of studies of dietary obesity. The effect of dietary variety on rat's intake led to studies of sensory-specific satiety in humans. In recent years the primary interest of my lab has been how food properties affect intake, satiety, and body weight. At the Johns Hopkins School of Medicine and now at The Pennsylvania State University, we have conducted systematic studies of the

effects of the macronutrients, variety, portion size, and energy density in both adults and children. Currently our research aims to understand how to leverage the robust effects of variety, portion size, and energy density to encourage healthy eating and drinking. Throughout my career I have been lucky to have been in supportive environments surrounded by creative, insightful, and diligent colleagues" (5).

8. Unexpected findings and promoting monocausal claims, a cautionary tale.

"Stories of serendipitous discoveries in medicine incorrectly imply that the path from an unexpected observation to major discovery is straightforward or guaranteed. In this paper, I examine a case from the field of research about chronic fatigue syndrome (CFS). In Norway, an unexpected positive result during clinical care has led to the development of a research programme into the potential for the immunosuppressant drug rituximab to relieve the symptoms of CFS. The media and public have taken up researchers' speculations that their research results indicate a causal mechanism for CFS - consequently, patients now have great hope that 'the cause' of CFS has been found, and thus, a cure is sure to follow. I argue that a monocausal claim cannot be correctly asserted, either on the basis of the single case of an unexpected, although positive, result or on the basis of the empirical research that has followed up on that result. Further, assertion and promotion of this claim will have specific harmful effects: it threatens to inappropriately narrow the scope of research on CFS, might misdirect research altogether, and could directly and indirectly harm patients. Therefore, the CFS case presents a cautionary tale, illustrating the risks involved in drawing a theoretical hypothesis from an unexpected observation. Further, I draw attention to the tendency in contemporary clinical research with CFS to promote new research directions on the basis of reductive causal models of that syndrome. Particularly, in the case of CFS research, underdetermination and causal complexity undermine the potential value of a monocausal claim. In sum, when an unexpected finding occurs in clinical practice or medical research, the value of following up on that finding is to be found not in the projected value of a singular causal relationship inferred from the finding but rather in the process of research that follows" (6).

9. Neuropharmacology beyond reductionism - A likely prospect.

Neuropharmacology had several major past successes, but the last few decades did not witness any leap forward in the drug treatment of brain

disorders. Moreover, current drugs used in neurology and psychiatry alleviate the symptoms, while hardly curing any cause of disease, basically because the etiology of most neuro-psychic syndromes is but poorly known. This review argues that this largely derives from the unbalanced prevalence in neuroscience of the analytic reductionist approach, focused on the cellular and molecular level, while the understanding of integrated brain activities remains flimsier. The decline of drug discovery output in the last decades, quite obvious in neuropharmacology, coincided with the advent of the single target-focused search of potent ligands selective for a well-defined protein, deemed critical in a given pathology. However, all the widespread neuro-psychic troubles are multi-mechanistic and polygenic, their complex etiology making unsuited the single-target drug discovery. An evolving approach, based on systems biology considers that a disease expresses a disturbance of the network of interactions underlying organismic functions, rather than alteration of single molecular components. Accordingly, systems pharmacology seeks to restore a disturbed network via multi-targeted drugs. This review notices that neuropharmacology in fact relies on drugs which are multi-target, this feature having occurred just because those drugs were selected by phenotypic screening in vivo, or emerged from serendipitous clinical observations. The novel systems pharmacology aims, however, to devise ab initio multi-target drugs that will appropriately act on multiple molecular entities. Though this is a task much more complex than the single-target strategy, major informatics resources and computational tools for the systemic approach of drug discovery are already set forth and their rapid progress forecasts promising outcomes for neuropharmacology (7).

10. Revolutionary Science.

On rare occasions in the history of science, remarkable discoveries transform human society and forever alter mankind's view of the world. Examples of such discoveries include the heliocentric theory, Newtonian physics, the germ theory of disease, quantum theory, plate tectonics and the discovery that DNA carries genetic information. The science philosopher Thomas Kuhn famously described science as long periods of normality punctuated by times of crisis, when anomalous observations culminate in revolutionary changes that replace one paradigm with another. This essay examines several transformative discoveries in the light of Kuhn's formulation. We find that each scientific revolution is unique, with disparate origins that may include puzzle solving, serendipity, inspiration, or a convergence of disparate observations.

The causes of revolutionary science are varied and lack an obvious common structure. Moreover, it can be difficult to draw a clear distinction between so-called normal and revolutionary science. Revolutionary discoveries often emerge from basic science and are critically dependent on nonrevolutionary research. Revolutionary discoveries may be conceptual or technological in nature, lead to the creation of new fields, and have a lasting impact on many fields in addition to the field from which they emerge. In contrast to political revolutions, scientific revolutions do not necessarily require the destruction of the previous order. For humanity to continue to benefit from revolutionary discoveries, a broad palette of scientific inquiry with a particular emphasis on basic science should be supported (8).

11. Trends in Modern Drug Discovery.

Drugs discovered by the pharmaceutical industry over the past 100 years have dramatically changed the practice of medicine and impacted on many aspects of our culture. For many years, drug discovery was a target- and mechanism-agnostic approach that was based on ethnobotanical knowledge often fueled by serendipity. With the advent of modern molecular biology methods and based on knowledge of the human genome, drug discovery has now largely changed into a hypothesis-driven target-based approach, a development which was paralleled by significant environmental changes in the pharmaceutical industry. Laboratories became increasingly computerized and automated, and geographically dispersed research sites are now more and more clustered into large centers to capture technological and biological synergies. Today, academia, the regulatory agencies, and the pharmaceutical industry all contribute to drug discovery, and, in order to translate the basic science into new medical treatments for unmet medical needs, pharmaceutical companies have to have a critical mass of excellent scientists working in many therapeutic fields, disciplines, and technologies. The imperative for the pharmaceutical industry to discover breakthrough medicines is matched by the increasing numbers of first-in-class drugs approved in recent years and reflects the impact of modern drug discovery approaches, technologies, and genomics (9).

12. (A) Historical science.

In contrast to many other human endeavors, science pays little attention to its history. Fundamental scientific discoveries are often considered to be timeless and independent of how they were made. Science and the history of science

are regarded as independent academic disciplines. Although most scientists are aware of great discoveries in their fields and their association with the names of individual scientists, few know the detailed stories behind the discoveries. Indeed, the history of scientific discovery is sometimes recorded only in informal accounts that may be inaccurate or biased for self-serving reasons. Scientific papers are generally written in a formulaic style that bears no relationship to the actual process of discovery. Here we examine why scientists should care more about the history of science. A better understanding of history can illuminate social influences on the scientific process, allow scientists to learn from previous errors, and provide a greater appreciation for the importance of serendipity in scientific discovery. Moreover, history can help to assign credit where it is due and call attention to evolving ethical standards in science. History can make science better (10).

13. The brain on itself: Nobel laureates and the history of fundamental nervous system function.

The Nobel Prize in Physiology or Medicine has been given in recognition of work in the neurosciences a number of times. Laureates have been awarded for work on both fundamental and more complex nervous system functions. This review is restricted to contributions by 20th century laureates to the understanding of fundamental nervous system function on the cellular level. In 1906, Camillo Golgi and Ramón y Cajal were awarded for their work on the microscopic structure of the nervous system. Their achievement and those of others within this field, coupled with technological progress, gradually allowed more complex physiological studies. In 1932, the prize was awarded to Charles Sherrington and Edgar Adrian for their discoveries of how neurons function. They were followed in 1944 by Herbert Gasser and Joseph Erlanger who uncovered the highly differentiated functions of single nerve fibers. Alan Hodgkin and Andrew Huxley were awarded for the detection of the ionic mechanism of the action potential and its mathematical explanation in 1963. In 1991, Erwin Neher and Bernd Sakmann were awarded for their work on single ion channels. Although the scientists who proved the hypothesis (Fridjof Nansen, Wilhelm His, and August Forel) were never awarded by the Nobel Committee, their studies gave rise to one of the most fundamental questions in 20th century neuroscience: How is information carried from one neuron to another or to an effector cell? This was first solved in the vegetative nervous system, and, in 1936, Henry Dale and Otto Loewi received the prize for their discoveries relating to chemical transmission of nerve impulses. In

1963, John Eccles was awarded the prize for his work on the physiology of synapses. In 1970, Bernhard Katz received the Nobel Prize for the discovery of quantal release. Katz shared the prize with Julius Axelrod and Ulf von Euler, who were central in finding that transmitters are stored in presynaptic vesicles and that the effect in many synapses is terminated by reuptake. This review does not include 21st century laureates, although the prize has already been given to neuroscientists twice this century; Arvid Carlsson, Paul Greengard, and Eric Kandel received the award in 2000 for their discoveries related to signal transduction, and Richard Axel and Linda Buck received the award in 2004 for their work in the field of odorant receptors and the organization of the olfactory system (11).

14. 'It was serendipity': a qualitative study of academic careers in medical education.

Despite a demand for educational expertise in medical universities, little is known of the roles of medical educators and the sustainability of academic careers in medical education. We examined the experiences and career paths of medical educators from diverse professional backgrounds seeking to establish, maintain and strengthen their careers in medical schools.

Semi-structured interviews were conducted with 44 lead and early-career medical educators from all 21 Australian and New Zealand medical schools. Questions explored career beginnings, rewards and challenges. Transcripts underwent systematic coding and independent thematic analysis. Final themes were confirmed by iterative review and member checking. Analysis was informed by Bourdieu's concepts of field (a social space for hierarchical interactions), habitus (individual dispositions which influence social interactions) and capital (economic, symbolic, social and cultural forms of power).

Participants provided diverse accounts of what constitutes the practice of medical education. Serendipitous career entry and little commonality of professional backgrounds and responsibilities suggest an ambiguous habitus with ill-defined career pathways. Within the field of medicine as enacted in medical schools, educators have invisible yet essential roles, experiencing tension between service expectations, a lesser form of capital, and demands for more highly valued forms of scholarship. Participants reported increasing expectations to produce research and obtain postgraduate qualifications to enter and maintain their careers. Unable to draw upon cultural capital accrued

from clinical work, non-clinician educators faced additional challenges. To strengthen their position, educators consciously built social capital through essential service relationships, capitalising on times when education takes precedence, such as curriculum renewal and accreditation.

Bourdieu's theory provides insight into medical educator career paths and the positioning of medical education within medical schools. Medical educators have an indistinct practice, and limited cultural capital in the form of research outputs. In order to maintain and strengthen their careers, educators must create alternative sources of capital, through fostering collaborative alliances (12).

15. The modern history and evolution of percutaneous nephrolithotomy.

Serendipity, innovative physicians, evolving techniques for renal access, and improvements in equipment and radiology led to the evolution of percutaneous nephrolithotomy (PCNL).

We searched urology texts and the literature for sources pertaining to the history and development of PCNL.

In 1941, Rupel and Brown performed the first nephroscopy when a rigid cystoscope was passed into the kidney following open surgery. Willard Goodwin, in 1955, while trying to perform a renal arteriogram, placed a needle into the collecting system of a hydronephrotic kidney and performed the first antegrade nephrostogram. He left a tube to drain the kidney, thereby placing the first nephrostomy tube. By 1976, Fernström and Johansson were the first to describe a technique for extracting renal calculi through a percutaneous nephrostomy under radiological control. In 1978, Arthur Smith, would describe the first antegrade stent placement when he introduced a Gibbons stent through a percutaneous nephrostomy in a patient with a reimplanted ureter. Dr. Smith would coin the term "endourology" to describe closed, controlled manipulation of the genitourinary tract. His collaboration with Kurt Amplatz, an interventional radiologist and medical inventor, would lead to numerous innovations that would further advance PCNL. In the 1980s the process of renal access and tract dilation was improved upon and the use of a rigid cystoscope was replaced by offset nephroscopes with a large straight working channel. Radiographic innovations, including improvements in fluoroscopy would further aid in renal access. The development of various lithotripsy devices and the introduction of the holmium laser improved the efficiency of stone fragmentation and clearance. The increased clinical experience and

utilization of PCNL would lead to the characterization of stone-free rates and complications for the procedure.

Serendipity, innovations in renal access, optics, radiology, and improvements in lithotripsy all contributed to the modern day PCNL (13).

16. History of the Buttonhole Technique.

The constant side method of access cannulation in hemodialysis, popularly known as the 'buttonhole' method, has an interesting history. Dr. Zbylut J. Twardowski, a Polish nephrologist, discovered this technique by pure serendipity in 1972. A patient with a complicated vascular access history and limited options for cannulation was repeatedly 'stuck' at the same sites by a nurse. Soon it was noticed that the cannulation at the same spot became easier with time. Since the needles were being reused, the sharpness of the needles decreased with time and the bluntness of the needle seemed to minimize the damage to the cannulation tract (another serendipity!). This method soon became popular among patients, and many patients started using this technique. This chapter traces the invention of this technique and its subsequent development following Dr. Twardowski's emigration to the USA (14).

17. Computer-Aided Drug Design of Bioactive Natural Products.

Natural products have been an integral part of sustaining civilizations because of their medicinal properties. Past discoveries of bioactive natural products have relied on serendipity, and these compounds serve as inspiration for the generation of analogs with desired physicochemical properties. Bioactive natural products with therapeutic potential are abundantly available in nature and some of them are beyond exploration by conventional methods. The effectiveness of computational approaches as versatile tools for facilitating drug discovery and development has been recognized for decades, without exception, in the case of natural products. In the post-genomic era, scientists are bombarded with data produced by advanced technologies. Thus, rendering these data into knowledge that is interpretable and meaningful becomes an essential issue. In this regard, computational approaches utilize the existing data to generate knowledge that provides valuable understanding for addressing current problems and guiding the further research and development of new natural-derived drugs. Furthermore, several medicinal plants have been continuously used in many traditional medicine systems since antiquity throughout the world, and their mechanisms have not yet been

elucidated. Therefore, the utilization of computational approaches and advanced synthetic techniques would yield great benefit to improving the world's health population and well-being (15).

18. To the centennial of Norman Holter (1914-1983).

The article is devoted to the centennial of the founder of ambulatory ECG monitoring Norman Jeffrey Holter (1914-1983). It contains brief history of the scientist's family, and depiction of his own educational way from magister of chemistry and physics to specialist in nuclear research. His activity during World War II, research related to impact of nuclear tests on environment after the war is also described. The fact is stressed that N. Holter was organizer and first president of Society of Nuclear Medicine. But most prominent contribution of N. Holter was elaboration of the method of long-term ECG monitoring of freely active patients--the method which was later named Holter Monitoring (HM). The article also contains data of first clinical trials of HM systems and stresses contribution of Holter team-mates and colleagues (B. Del Mar, G. Kennedy, S. Stern and others) in their conduct. It shows technical and ideological evolution of HM systems from large apparatuses weighting 40 kg to modern portable devices capable of collecting, storing and processing huge amounts of information, transmitting it over internet to any distance. Nontriviality and serendipity of N. Holter's approach to obtaining novel unpredictable knowledge allowed him to realize his numerous talents and abilities (16).

19. Lost in Translation (LiT): IUPHAR Review 6.

Translational medicine is a roller coaster with occasional brilliant successes and a large majority of failures. Lost in Translation 1 ('LiT1'), beginning in the 1950s, was a golden era built upon earlier advances in experimental physiology, biochemistry and pharmacology, with a dash of serendipity, that led to the discovery of many new drugs for serious illnesses. LiT2 saw the large-scale industrialization of drug discovery using high-throughput screens and assays based on affinity for the target molecule. The links between drug development and university sciences and medicine weakened, but there were still some brilliant successes. In LiT3, the coverage of translational medicine expanded from molecular biology to drug budgets, with much greater emphasis on safety and official regulation. Compared with R&D expenditure, the number of breakthrough discoveries in LiT3 was disappointing, but monoclonal antibodies for immunity and inflammation

brought in a new golden era and kinase inhibitors such as imatinib were breakthroughs in cancer. The pharmaceutical industry is trying to revive the LiT1 approach by using phenotypic assays and closer links with academia. LiT4 faces a data explosion generated by the genome project, GWAS, ENCODE and the 'omics' that is in danger of leaving LiT4 in a computerized cloud. Industrial laboratories are filled with masses of automated machinery while the scientists sit in a separate room viewing the results on their computers. Big Data will need Big Thinking in LiT4 but with so many unmet medical needs and so many new opportunities being revealed there are high hopes that the roller coaster will ride high again (17).

20. Clinical research and the development of medical therapeutics.

Clinical research plays a central role in the development of medical therapeutics, but the current system is estimated to take 10-15 years from initial discovery to regulatory approval, at a cost of approximately US\$1 billion. Contrast the paths by which 2 anticoagulant options for atrial fibrillation were discovered and ultimately established as treatment options in clinical medicine. Warfarin was discovered by serendipity and compared with placebo in relatively small trials; this was associated with a low cost of development. The new oral anticoagulants were synthesized to provide highly specific, targeted inhibition of critical steps in the coagulation system. They were compared with warfarin for prevention of stroke and systemic embolic events in large, phase 3 trials; this resulted in very expensive development programs. Neither of these paths is desirable for future development of therapeutics. We need to focus on innovative approaches at the preclinical level (systems approach, greater use of inducible pluripotent stem cells, use of novel bioengineering platforms) and clinical trial level (adaptive design, greater use of new and emerging technology). Focusing on disruptive innovations for development of medical therapeutics has the potential to bring us closer to the goal of precision medicine where safer, more effective treatments are discovered in a more efficient system (18).

21. The whole is more than the sum of its parts: Aristotle, metaphysical.

This phrase, a favorite of Dr. Joseph E. Murray, can be interpreted in many ways. Mathematically, the whole is equal to the sum of its parts, neither more nor less. Psychological Gestalt theory would maintain that the whole is something else or something different than the sum of its parts. Merely adding up the component parts is meaningless compared with the "part-whole"

relationship (SYNERGETICS: Explorations of Thinking. MacMillan Publishing Co, Inc; 1975). Organizational pundits maintain that this principle describes the synergy, which exists between individuals working together in a cooperative effort. Collectively, they are able to achieve an outcome superior to that of 1 or 2 people working alone. This concept is vintage Joseph E. Murray. He was an integral part of the Peter Bent Brigham team, which transformed the dream of organ transplantation into clinical reality over 50 years ago. Although many advances in medicine are made by the serendipity of a prepared mind making a critical observation (Alexander Fleming and penicillin), individual brilliance (Judah Folkman and angiogenesis), or by technology (magnetic resonance imaging), most are achieved by groups of physicians and scientists working together. All have prepared minds. When the Peter Bent Brigham Hospital physicians and researchers at the Harvard Medical School dedicated all of their energy on solving the problems of end-stage renal disease, their effort was concentrated and primarily regional. Today, this cooperation is global, as communication has been facilitated by the Internet, iPhone, iPad, video conferencing, electronic libraries, and the like (19).

22. The maternal-to-zygotic transition targets actin to promote robustness during morphogenesis.

Robustness is a property built into biological systems to ensure stereotypical outcomes despite fluctuating inputs from gene dosage, biochemical noise, and the environment. During development, robustness safeguards embryos against structural and functional defects. Yet, our understanding of how robustness is achieved in embryos is limited. While much attention has been paid to the role of gene and signaling networks in promoting robust cell fate determination, little has been done to rigorously assay how mechanical processes like morphogenesis are designed to buffer against variable conditions. Here we show that the cell shape changes that drive morphogenesis can be made robust by mechanisms targeting the actin cytoskeleton. We identified two novel members of the Vinculin/ α -Catenin Superfamily that work together to promote robustness during *Drosophila* cellularization, the dramatic tissue-building event that generates the primary epithelium of the embryo. We find that zygotically-expressed Serendipity- α (Sry- α) and maternally-loaded Spitting Image (Spt) share a redundant, actin-regulating activity during cellularization. Spt alone is sufficient for cellularization at an optimal temperature, but both Spt plus Sry- α are required

at high temperature and when actin assembly is compromised by genetic perturbation. Our results offer a clear example of how the maternal and zygotic genomes interact to promote the robustness of early developmental events. Specifically, the Spt and Sry- α collaboration is informative when it comes to genes that show both a maternal and zygotic requirement during a given morphogenetic process. For the cellularization of *Drosophilids*, Sry- α and its expression profile may represent a genetic adaptive trait with the sole purpose of making this extreme event more reliable. Since all morphogenesis depends on cytoskeletal remodeling, both in embryos and adults, we suggest that robustness-promoting mechanisms aimed at actin could be effective at all life stages (20).

23. The pipeline in headache therapy.

Migraine is a common, disabling, neurovascular disorder characterized by episodic attacks of head pain and associated disability plus systemic autonomic and neurologic symptoms. The advent of the triptan class of medication in the 1990s revolutionized the acute treatment of migraine, but many migraineurs do not respond optimally or at all to triptans, have intolerable adverse effects, or have contraindications to their use. Preventive pharmacotherapy has advanced mostly through serendipity, with new drugs being found effective while being used for other indications. There remains a significant need for new medications and devices that can provide effective, rapid, and sustained pain relief without adverse effects or recurrence. Several new acute and preventive therapies for the treatment of migraine and cluster headaches have shown promise and are currently under investigation. This article covers innovative delivery mechanisms, calcitonin gene-related peptide receptor antagonists, antibodies to calcitonin gene-related peptide and its receptor, 5-HT_{1F} receptor agonists, transient receptor potential vanilloid receptor modulators, orexin receptor antagonists, glial cell modulators, and neurostimulation (21).

24. Editorial: from correlations to causation: the value of preventive interventions in studying pathogenic mechanisms in childhood psychiatric disorders.

The ultimate goal of all research in childhood psychiatric disorders is to provide knowledge that will be useful in treating or preventing illness. To be useful in treating or preventing illness, research studies must provide valid information about the causes of illness, because only by targeting those causes can we prevent or counter their effects in a truly rational way. Until

now, the discovery of interventions has largely been by serendipity, yielding medications and behavioral interventions that produce too little therapeutic response, in too few people, and with too many side effects. The selection of which specific intervention to use for which child is based on trial-and-error guesswork and the personal preferences and idiosyncrasies of the treating clinician, with little or no empirical support, and at great cost to children, families, and health care systems. Guesswork in treatment will decline only when we have more detailed knowledge of the differing causal pathways that produce differing subtypes of the same disease phenotype. Identifying more homogeneous subtypes of disease that have more uniform natural histories and treatment responses will permit development of more genuinely rational and individualized interventions, or more truly personalized medicine . Identifying causal pathways in human disease, however, is especially challenging because the classic method of experimental investigation - isolating and manipulating at will a variable that is hypothesized to exert a causal influence on the illness in order to understand its effects on other variables - is not possible when studying the causes of human illness, for obvious ethical reasons. We are therefore left with a variety of methods for identifying probable causal pathways in human illness, all of which have varying strengths and limitations in the weight of evidence that they provide that a variable has a true causal influence on the disorder (22).

25. Ellis-van Creveld syndrome: its history.

The story of Ellis-van Creveld syndrome is one of serendipity. By chance, Simon van Creveld and Richard Ellis purportedly met on a train and combined their independently encountered patients with short stature, dental anomalies and polydactyly into one landmark publication in 1940. They included a patient used in work published previously by Rustin McIntosh without naming McIntosh as a coauthor. This patient was followed radiologically by Caffey for nearly two decades. In 1964, Victor McKusick felt compelled to investigate a brief report in an obscure pharmaceutical journal on an unusual geographic cluster of short-statured Amish patients in Pennsylvania. This review highlights the lives of the individuals involved in the discovery of Ellis-van Creveld syndrome in their historic context (23).

26. International women physicians' perspectives on choosing an academic medicine career.

Concerns about recruiting physicians into academic careers is an international issue. A qualitative study with United States (US) women physicians revealed

insights into how, when, and why physicians choose an academic career in medicine. The current study explored international women physicians' perspectives on their career choice of academic medicine and determined if different themes emerged. We expanded the 2012 study of US women physicians by interviewing women physicians in Canada, Pakistan, Mexico, and Sweden to gain an international perspective on choosing an academic career. Interviews were thematically analyzed against themes identified in the previous study. Based on themes identified in the study of US physicians, qualitative analysis of 7 international women physicians revealed parallel themes for the following areas: Why academic medicine? Fit; People; Aspects of academic health centre environment. How the decision to enter academic medicine was made? Decision-making style; Emotionality When the decision to enter academic medicine was made? Practising physician; Fellowship; Medical student. Work-life balance, choosing academic medicine by default, serendipity, intellectual stimulation, mentors, research and teaching were among the areas specifically highlighted.

Parallel themes exist regarding how, why, and when US and international women physicians choose academic medicine as a career path (24).

27. Chronic diarrhea as the presenting feature of primary systemic AL amyloidosis: serendipity or delayed diagnosis?

Chronic diarrhea in adults is a common symptom with a wide range of underlying etiologies. Although various strategies have been proposed for evaluation, there are still cases with undetermined origins even after extensive workup. Amyloidosis with gastrointestinal (GI) involvement is one of the causes that should be considered in adult patients with chronic diarrhea. We report a case of primary systemic amyloid light-chain (AL) amyloidosis, presenting initially as chronic diarrhea and weight loss.

A 43-year-old man with chronic diarrhea and weight loss was referred to our hospital. Prior to his presentation, extensive evaluation including an exploratory laparotomy was carried out and did not yield any valuable findings. An echocardiography performed after repeated episodes of orthostatic hypotension revealed infiltrative cardiomyopathy. Moreover, biopsies of the terminal ileum revealed amyloid deposition confirmed by Congo Red staining. Finally, a diagnosis of systemic AL amyloidosis was made after hematological workup. Anti-plasma cell therapy did ameliorate his GI symptoms.

Although amyloidosis with GI involvement is a rare cause of chronic diarrhea, it should be considered especially in patients with intestinal malabsorption and extra-GI manifestations, such as orthostatic hypotension. The delayed diagnosis in the present case highlights the importance of recognizing clinical "red flags" not seemingly related to one another, and underscores the need to get intestinal biopsies even with normal endoscopic appearance of the mucosa (25).

28. Paradoxical Sost gene expression response to mechanical unloading in metaphyseal bone.

The Sost gene encodes Sclerostin, an inhibitor of Wnt-signaling, generally considered a main response gene to mechanical loading in bone. Several papers describe that unloading leads to upregulation of Sost, which in turn may lead to loss of bone. These studies were based on whole bone homogenates or cortical bone. By serendipity, we noted an opposite response to unloading in the proximal rat tibia. Therefore, we hypothesized that Sost-expression in response to changes in mechanical load is bone site specific. One hind limb of male, 3 month old rats was unloaded by paralyzing the extensors with Botulinium toxin A (Botox) injections. A series of experiments compared the expression of Sost mRNA in the unloaded and contralateral, loaded limbs, after 3 or 10 days, in metaphyseal cancellous bone, metaphyseal cortical bone, and diaphyseal cortical bone. We also conducted μ CT to confirm changes in bone volume density related to unloading. Sost mRNA expression in the cancellous metaphyseal bone was downregulated almost 2-fold, both 3 days and 10 days after unloading ($P < 0.05$). A similar tendency was seen in the metaphyseal cortical bone, in which Sost was 1.5-fold downregulated ($P < 0.05$) after 10 days, but not significantly changed after 3 days. In contrast, diaphyseal cortical Sost expression was instead upregulated 1.4-fold ($P < 0.05$) following 3-day unloading, while there was no significant change after 10 days. Cancellous bone volume density was 58% lower ($P < 0.001$, compared to cage controls) in the unloaded limb but not significantly affected in the loaded limb. The results suggest that Sost mRNA expression in metaphyseal bone responds to mechanical unloading in an opposite direction to that observed in diaphyseal cortical bone. This proposes a more complex expression pattern for Sost in response to unloading. Therapeutics that target Sclerostin during altered loading conditions may result in local bone mass changes that are difficult to predict (26).

29. Fate of intravenously injected mesenchymal stem cells and significance for clinical application.

Mesenchymal stromal cells (MSCs) have initially been characterized as a fibroblastlike cell population that can be expanded readily in vitro, and is able to support hematopoiesis in vitro and in vivo. By serendipity it was discovered that MSCs can also be administered into the bloodstream. This mode of application formed a major breakthrough in the clinical use of MSCs, because MSC transplantation was found to cure severe immune hyperactivation states such as graft-versus-host disease after allogeneic bone marrow transplantation, or bacterial sepsis. However, MSCs were found difficult to trace and consensus to date is lacking in the scientific community as to where transplanted MSCs end up in the body and which major principles are responsible for the therapeutic effects of MSCs. This chapter gives an overview of the current knowledge on interactions of freshly transplanted MSCs with the cells in the blood stream and the vessel wall, with major organs such as lung, liver, gut, and spleen, and discusses the limitations of the methodologies used to trace transplanted MSCs. The findings will be put into perspective on how therapeutically applied, culture-expanded MSCs may exert beneficial effects (27).

30. Tools for innovative thinking in epidemiology.

Innovation is the engine of scientific progress. Concern has been raised by the National Academies of Science about how well America is sustaining its "creative ecosystem." In this commentary, the author argues that we can all improve our ability to think innovatively through instruction and practice. The author presents a series of tools that are currently being taught in a curriculum developed at the University of Texas, based on earlier evidence-based creativity training programs. The tools are these: 1) finding the right question; 2) enhancing observation; 3) using analogies; 4) juggling induction and deduction; 5) changing your point of view; 6) broadening the perspective; 7) dissecting the problem; 8) leveraging serendipity and reversal; 9) reorganization and combination of ideas; 10) getting the most out of groups; and 11) breaking out of habitual expectations and frames. Each tool is explained using examples from science and public health. It is likely that each of us will identify with and agree with the usefulness of one or two of the tools described. Broader mastery of many of these tools, particularly when used in combination, has provided our students with a powerful device for enhancing innovation (28).

31. Ferruccio Ritossa's scientific legacy 50 years after his discovery of the heat shock response: a new view of biology, a new society, and a new journal.

The pioneering discovery of the heat shock response by the Italian scientist Ferruccio Ritossa reached maturity this year, 2012. It was 50 years ago that Professor Ritossa, through an extraordinary combination of serendipity, curiosity, knowledge and inspiration, published the first observation that cells could mount very strong transcriptional activity when exposed to elevated temperatures, which was coined the heat shock response. This discovery led to the identification of heat shock proteins, which impact many areas of current biology and medicine, and has created a new avenue for more exciting discoveries. In recognition of the discovery of the heat shock response, Cell Stress Society International (CSSI) awarded Professor Ritossa with the CSSI medallion in October 2010 in Dozza, Italy (29).

32. The discovery and development of belimumab: the anti-BLyS-lupus connection.

For the first time in more than 50 years, the US Food and Drug Administration has approved a drug specifically for the treatment of systemic lupus erythematosus (SLE). This drug, belimumab (Benlysta), is a human monoclonal antibody that neutralizes the B-cell survival factor, B-lymphocyte stimulator (BLyS). The approval of belimumab combined a pioneering approach to genomics-based gene discovery, an astute appreciation of translational medicine, a disciplined clinical strategy, a willingness to take calculated risks, a devoted cadre of patients and physicians and a healthy dose of serendipity. Collectively, these efforts have provided a model for the development of a new generation of drugs to treat the broad manifestations of SLE. However, as a substantial percentage of SLE patients do not respond to belimumab, further research is needed to better characterize the pathogenetic mechanisms of SLE, identify additional therapeutic targets, and develop effective and nontoxic novel agents against these targets (30).

33. Earthworms dilong: ancient, inexpensive, noncontroversial models may help clarify approaches to integrated medicine emphasizing neuroimmune systems.

Earthworms have provided ancient cultures with food and sources of medicinal cures. Ayurveda, traditional Chinese medicine (TCM), and practices in Japan, Vietnam, and Korea have focused first on earthworms as sources of food. Gradually fostering an approach to potential beneficial healing

properties, there are renewed efforts through bioprospecting and evidence-based research to understand by means of rigorous investigations the mechanisms of action whether earthworms are used as food and/or as sources of potential medicinal products. Focusing on earthworms grew by serendipity from an extensive analysis of the earthworm's innate immune system. Their immune systems are replete with leukocytes and humoral products that exert credible health benefits. Their emerging functions with respect to evolution of innate immunity have long been superseded by their well-known ecological role in soil conservation. Earthworms as inexpensive, noncontroversial animal models (without ethical concerns) are not vectors of disease do not harbor parasites that threaten humans nor are they annoying pests. By recognizing their numerous ecological, environmental, and biomedical roles, substantiated by inexpensive and more comprehensive investigations, we will become more aware of their undiscovered beneficial properties (31).

34. Serendipity in anticancer drug discovery.

It was found that the discovery of 5.8% (84/1437) of all drugs on the market involved serendipity. Of these drugs, 31 (2.2%) were discovered following an incident in the laboratory and 53 (3.7%) were discovered in a clinical setting. In addition, 263 (18.3%) of the pharmaceuticals in clinical use today are chemical derivatives of the drugs discovered with the aid of serendipity. Therefore, in total, 24.1% (347/1437) of marketed drugs can be directly traced to serendipitous events confirming the importance of this elusive phenomenon. In the case of anticancer drugs, 35.2% (31/88) can be attributed to a serendipitous event, which is somewhat larger than for all drugs. The therapeutic field that has benefited the most from serendipity are central nervous system active drugs reflecting the difficulty in designing compounds to pass the blood-brain-barrier and the lack of laboratory-based assays for many of the diseases of the mind (32).

35. Serendipity and its role in dermatology.

Serendipity is a pleasant surprise of finding a particularly useful information while not looking for it. Significant historic events occurring as a result of serendipity include the discovery of the law of buoyancy (Archimedes principle) by the Greek mathematician Archimedes, of the Americas by Christopher Columbus and of gravity by Sir Isaac Newton. The role of serendipity in science has been immensely beneficial to mankind. A host of

important discoveries in medical science owe their origin to serendipity of which perhaps the most famous is the story of Sir Alexander Fleming and his discovery of Penicillin. In the field of dermatology, serendipity has been responsible for major developments in the therapy of psoriasis, hair disorders, aesthetic dermatology and dermatosurgery. Besides these many other therapeutic modalities in dermatology were born as a result of such happy accidents (33).

36. Serendipity in Relationship: A Tentative Theory of the Cognitive Process of Yuanfen and Its Psychological Constructs in Chinese Cultural Societies.

The main purpose of this article is to combine three important themes in Chinese cultural societies: serendipity in relationship (yuanfen), relational interactions, and psychological adaptation through self-cultivation. People who live in Chinese cultural societies are deeply affected by relationalism and tend to be very different from their Western counterparts, who adopt individualistic methods when dealing with interpersonal problems. They are highly likely to access the perspective of yuanfen as part of their cultural wisdom to convert negative feelings, awkwardness, or setbacks caused by interpersonal relationship incidents, into a type of cognitive belief that can be used to combat anxiety and actuate coping actions. Based on this, this article proposes the tentative theory of a dialectical model which comprises elements of the philosophies of Daoism, Buddhism and Confucianism, to analyze the cognitive operation process regarding yuanfen and to explain and predict how people in Chinese cultural societies differ from most Western people in terms of psychological adjustment and coping actions when dealing with interpersonal problems. Canonical correlation analysis was used in the empirical study to describe this model and resulted in two statistically significant canonical factor pairs. The hypothesized model has been partially verified. It is hoped that this framework can serve as a pilot perspective for future studies, and at the same time provide the Western academic world with a reference for understanding the concept and substantive effects of serendipity in relationship (34).

37. QUADRATIC SERENDIPITY FINITE ELEMENTS ON POLYGONS USING GENERALIZED BARYCENTRIC COORDINATES.

We introduce a finite element construction for use on the class of convex, planar polygons and show it obtains a quadratic error convergence estimate. On a convex n -gon, our construction produces $2n$ basis functions, associated

in a Lagrange-like fashion to each vertex and each edge midpoint, by transforming and combining a set of $n(n + 1)/2$ basis functions known to obtain quadratic convergence. The technique broadens the scope of the so-called 'serendipity' elements, previously studied only for quadrilateral and regular hexahedral meshes, by employing the theory of generalized barycentric coordinates. Uniform *a priori* error estimates are established over the class of convex quadrilaterals with bounded aspect ratio as well as over the class of convex planar polygons satisfying additional shape regularity conditions to exclude large interior angles and short edges. Numerical evidence is provided on a trapezoidal quadrilateral mesh, previously not amenable to serendipity constructions, and applications to adaptive meshing are discussed (35).

38. Curious discoveries in antiviral drug development: the role of serendipity.

Antiviral drug development has often followed a curious meandering route, guided by serendipity rather than rationality. This will be illustrated by ten examples. The polyanionic compounds (i) polyethylene alanine (PEA) and (ii) suramin were designed as an antiviral agent (PEA) or known as an antitrypanosomal agent (suramin), before they emerged as, respectively, a depilatory agent, or reverse transcriptase inhibitor. The 2',3'-dideoxynucleosides (ddNs analogues) (iii) have been (and are still) used in the "Sanger" DNA sequencing technique, although they are now commercialized as nucleoside reverse transcriptase inhibitors (NRTIs) in the treatment of HIV infections. (E)-5-(2-Bromovinyl)-2'-deoxyuridine (iv) was discovered as a selective anti-herpes simplex virus compound and is now primarily used for the treatment of varicella-zoster virus infections. The prototype of the acyclic nucleoside phosphonates (ANPs), (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine [(S)-HPMPA], (v) was never commercialized, although it gave rise to several marketed products (cidofovir, adefovir, and tenofovir). 1-[2-(Hydroxyethoxy)methyl]-6-(phenylthio)thymine (vi) and TIBO (tetrahydroimidazo[4,5,1-jk][1,4-benzodiazepin-2(1H)]-one and -thione) (vii) paved the way to a number of compounds (i.e., nevirapine, delavirdine, etravirine, and rilpivirine), which are now collectively called non-NRTIs. The bicyclam AMD3100 (viii) was originally described as an anti-HIV agent before it became later marketed as a stem cell mobilizer. The S-adenosylhomocysteine hydrolase inhibitors (ix), while active against a broad range of (-)RNA viruses and poxviruses may be particularly effective against

Ebola virus, and for (x) the O-ANP derivatives, the potential application range encompasses virtually all DNA viruses (36).

39. Serendipity in Cancer Drug Discovery: Rational or Coincidence?

Novel drug development leading to final approval by the US FDA can cost as much as two billion dollars. Why the cost of novel drug discovery is so expensive is unclear, but high failure rates at the preclinical and clinical stages are major reasons. Although therapies targeting a given cell signaling pathway or a protein have become prominent in drug discovery, such treatments have done little in preventing or treating any disease alone because most chronic diseases have been found to be multigenic. A review of the discovery of numerous drugs currently being used for various diseases including cancer, diabetes, cardiovascular, pulmonary, and autoimmune diseases indicates that serendipity has played a major role in the discovery. In this review we provide evidence that rational drug discovery and targeted therapies have minimal roles in drug discovery, and that serendipity and coincidence have played and continue to play major roles (37).

40. The role of serendipity in the discovery of the clinical effects of psychotropic drugs: beyond of the myth.

The serendipity is the faculty for making a discovery through a combination of accident and sagacity. In psychopharmacology, the serendipity played a key role in the discovery of many psychotropic drugs, although there are marked disputes in this regard, possibly due to semantic differences in relation to the meaning of this term. We have implemented an operational definition of serendipity based on the discovery of something unexpected or not sought intentionally, irrespective of the systematic process leading to the accidental observation. The present paper analyses some representative examples of discoveries in the field of psychopharmacology according to different serendipitous intervention patterns. Following this approach there would be four different imputability patterns: pure serendipitous discoveries (valproic acid/valproate); serendipitous observation leading to a non-serendipitous discoveries (imipramine); non-serendipitous discoveries secondarily associated with serendipitous observation (barbiturates); non-serendipitous discoveries (haloperidol). We can conclude that pure serendipitous discoveries in this field are not very frequent, most common being a mixed pattern; an initial serendipitous observation which leads to a non-serendipitous discovery of clinical utility. This is the case of imipramine, lithium salts, chlorpromazine or meprobamate (38).

41. Pluripotency and the endogenous retrovirus HERVH: Conflict or serendipity?

Remnants of ancient retroviral infections during evolution litter all mammalian genomes. In modern humans, such endogenous retroviral (ERV) sequences comprise at least 8% of the genome. While ERVs and other types of transposable elements undoubtedly contribute to the genomic "junk yard", functions for some ERV sequences have been demonstrated, with growing evidence that ERVs can be important players in gene regulatory processes. Here we focus on one particular large family of human ERVs, termed HERVH, which several recent studies suggest has a key regulatory role in human pluripotent stem cells. Remarkably, this is not the first instance of an ERV controlling pluripotency. We speculate as to why this convergent evolution might have come about, suggesting that it may reflect selection on the virus to extend the time available for transposition. Alternatively it may reflect serendipity alone (39).

42. Muller glia, vision-guided ocular growth, retinal stem cells, and a little serendipity: the Cogan lecture.

Hypothesis-driven science is expected to result in a continuum of studies and findings along a discrete path. By comparison, serendipity can lead to new directions that branch into different paths. Herein, I describe a diverse series of findings that were motivated by hypotheses, but driven by serendipity. I summarize how investigations into vision-guided ocular growth in the chick eye led to the identification of glucagonergic amacrine cells as key regulators of ocular elongation. Studies designed to assess the impact of the ablation of different types of neurons on vision-guided ocular growth led to the finding of numerous proliferating cells within damaged retinas. These proliferating cells were Müller glia-derived retinal progenitors with a capacity to produce new neurons. Studies designed to investigate Müller glia-derived progenitors led to the identification of a domain of neural stem cells that form a circumferential marginal zone (CMZ) that lines the periphery of the retina. Accelerated ocular growth, caused by visual deprivation, stimulated the proliferation of CMZ progenitors. We formulated a hypothesis that growth-regulating glucagonergic cells may regulate both overall eye size (scleral growth) and the growth of the retina (proliferation of CMZ cells). Subsequent studies identified unusual types of glucagonergic neurons with terminals that ramify within the CMZ; these cells use visual cues to control equatorial ocular growth and the proliferation of CMZ cells. Finally, while studying the signaling pathways that stimulate

CMZ and Müller glia-derived progenitors, serendipity led to the discovery of a novel type of glial cell that is scattered across the inner retinal layers (40).

43. Serendipity in the diagnosis of pheochromocytoma.

Pheochromocytomas are increasingly being discovered incidentally on imaging studies performed without clinical suspicion of the existence of an adrenal lesion. We aimed to determine the rate of diagnosis of adrenal pheochromocytoma as an incidental finding during a recent 7-year period.

We obtained the Department of Pathology database to study all the patients at our institution with newly diagnosed pheochromocytomas in the 7-year period from 2005 to 2011 to determine the clinical presentation and the means of diagnosis.

In 40 (70.2%) of the 57 patients, an adrenal pheochromocytoma was detected in an imaging study performed without suspicion of an adrenal lesion. There were 13 chest computed tomography studies-8 to evaluate for possible pulmonary emboli. Other indications included abdominal pain or discomfort (n = 8), trauma (n = 3), abnormal liver function tests (n = 3), suspect renal artery stenosis (n = 3), hematuria (n = 2), colitis (n = 2), and 4 miscellaneous indications.

Our study documents that the commonest current means of initial detection of pheochromocytoma is by serendipitous discovery. In 16 of our 40 patients with serendipitously discovered pheochromocytomas, there were no clinical symptoms of pheochromocytoma; these were true incidentalomas. More than two thirds of the new cases of pheochromocytoma were detected by serendipity (found during studies not performed to evaluate for pheochromocytoma), approximately one third were true incidentalomas (pheochromocytomas in patients without symptoms).

In a 7-year period at a single institution, 40 patients, 70% of new cases of surgically proven pheochromocytoma, were initially detected by serendipity. Sixteen patients, 40% of those incidentally discovered represented true examples of "incidentalomas." (41).

44. Highly Effective New Treatments for Psoriasis Target the IL-23/Type 17 T Cell Autoimmune Axis.

Psoriasis vulgaris, affecting the skin, is one of the most common organ-specific autoimmune diseases in humans. Until recently, psoriasis was treated by agents or approaches discovered largely through serendipity. Many of the

available drugs were inherently quite toxic when used as continuous treatment for many years in this chronic disease. However, an increasing understanding of disease-specific immune pathways has spurred development of pathway-targeted therapeutics during the past decade. Psoriasis is now the most effectively treated human autoimmune disease, with high-level clinical improvements possible in ~90% of patients using a new generation of drugs that selectively target the IL-23/Type 17 T cell axis. Thus, psoriasis is a model for the success of a translational-medicine approach based on cellular and molecular dissection of disease pathogenesis in humans (42).

45. History of growth hormone therapy.

The first human to receive GH therapy was in 1956; it was of bovine origin and was given for 3 wk for metabolic balance studies revealing no effects. By 1958, three separate laboratories utilizing different extraction methods retrieved hGH from human pituitaries, purified it and used for clinical investigation. By 1959 presumed GHD patients were being given native hGH collected and extracted by various methods. Since 1 mg of hGH was needed to treat one patient per day, >360 human pituitaries were needed per patient per year. Thus, the availability of hGH was limited and was awarded on the basis of clinical research protocols approved by the National Pituitary Agency (NPA) established in 1961. hGH was dispensed and injected on a milligram weight basis with varied concentrations between batches from 0.5 units/mg to 2.0 units/mg of hGH. By 1977 a centralized laboratory was established to extract all human pituitaries in the US, this markedly improved the yield of hGH obtained and most remarkably, hGH of this laboratory was never associated with Creutzfeld-Jacob disease (CJD) resulting from the injection of apparently prior-contaminated hGH produced years earlier. However, widespread rhGH use was not possible even if a pituitary from each autopsy performed in the US was collected, this would only permit therapy for about 4,000 patients. Thus, the mass production of rhGH required the identification of the gene structure of the hormone, methodology that began in 1976 to make insulin by recombinant technology. Serendipity was manifest in 1985 when patients who had received hGH years previously were reported to have died of CJD. This led to the discontinuation of the distribution and use of hGH, at a time when a synthetic rhGH became available for clinical use. The creation of a synthetic rhGH was accompanied by unlimited supplies of hGH for investigation and therapy. However, the appropriate use and the potential

abuse of this hormone are to be dealt with. The illegitimate use of rhGH, unequivocally the abuse by athletes is, and should be, of primary concern to society and should be halted. The abuse of prescribing rhGH in an attempt to retard the aging process also should receive attention (43).

46. Chance and serendipity in science: two examples from my own career.

The usual scientific paper follows a rather narrowly (but not ever rigidly) defined pattern. Both the author and the journal like to see a linear logical presentation of a "story." Seldom does the paper give the reader the "backstory." Where did the idea come from in the first place? How many false leads led down blind alleys? What happened by chance and what by logical planning? Was there an element of serendipity involved? Perhaps as we enter the paperless era and do not have to count words quite so religiously, it may be possible to encourage a more freewheeling scientific paper, but for now, we have to rely on the historians of science and/or those who "tell all" about their own research. "Reflections" seems an appropriate space for the latter. (44).

47. Diabetes-science, serendipity and common sense.

This paper is dedicated to young researchers in diabetes. One such person was Frederick Banting who, with his colleagues, isolated insulin in 1921, saving the lives of literally millions of people. What factors allowed Banting and other scientists to produce work that has immensely benefited the human race? I propose that it is the combination of good scientific background (the 'prepared mind'), commonly some serendipity taken with a good dose of common sense and supplemented by enthusiasm, tenacity and good mentoring, which drives the 'power of observation' and the ability to take forward the good idea. I give examples from history to support this and then discuss some of the 'truths, perspectives and controversies' within the diabetes arena when I first started in diabetes research in the late 1970s. I describe how my appetite was initially 'whetted' for research by moving to an excellent clinical research environment with encouragement to test ideas and controversies initially in a clinical research programme, followed by more scientific/basic research. The work that I performed as a young doctor and research fellow led to a lifelong professional interest in three major areas- causes and interventions for diabetes vascular disease, studies of the molecular genetics of Type 1 and Type 2 diabetes and work on diabetes in different ethnic groups. I provide a summation of my own and other people's

work to demonstrate how research can be progressed and lead to patient benefit as well as providing an incredibly rewarding career. I believe that we need to encourage and put more resources into development of young doctors and scientists wishing to undertake research in our discipline. Areas ripe for much-needed clinical research programmes, for example, include work on best practice/provision of health care, application of the evidence base from clinical trials to achieve public health gains, attention to adherence issues and better-tolerated therapies. Most importantly, a greater emphasis on prevention through public health measures and 'buy in' from the whole population is urgently required (45).

48. Bioinorganics and biomaterials: bone repair.

The field of bioinorganics is well established in the development of a variety of therapies. However, their application to bone regeneration, specifically by way of localized delivery from functional implants, is in its infancy and is the topic of this review. The toxicity of inorganics is species, dose and duration specific. Little is known about how inorganic ions are effective therapeutically since their use is often the result of serendipity, observations from nutritional deficiency or excess and genetic disorders. Many researchers point to early work demonstrating a role for their element of interest as a micronutrient critical to or able to alter bone growth, often during skeletal development, as a basis for localized delivery. While one can appreciate how a deficiency can cause disruption of healing, it is difficult to explain how a locally delivered excess in a preclinical model or patient, which is presumably of normal nutritional status, can evoke more bone or faster healing. The review illustrates that inorganics can positively affect bone healing but various factors make literature comparisons difficult. Bioinorganics have the potential to have just as big an impact on bone regeneration as recombinant proteins without some of the safety concerns and high costs (46).

49. Fluorescein angiography: insight and serendipity a half century ago.

It has been 50 years since fluorescein angiography was developed as a clinical procedure by 2 medical students at Indiana University. The story of its discovery and the recognition of its value to ophthalmology involve a combination of insight and serendipity. Fluorescein had been in use clinically for more than half a century, but it took a pulmonary medicine laboratory to provide the stimulus for the development of flash and barrier filters that would make vascular photography practical. The first article was rejected by the

ophthalmology literature, but several clinics heard about it and soon documented the enormous diagnostic value of the procedure (47).

50. The discovery of endothelin: the power of bioassay and the role of serendipity in the discovery of endothelium-derived vasocative substances.

Significant discoveries in biology and medicine are rare. The progress in these fields is predominantly incremental, but sometimes new observations revolutionize the field by opening new directions in research for decades to come. Two cornerstone observations in the late 1970s and early 1980s are examples of such "revolutionary" events. The first, by Furchgott and Zawadzki, was the discovery of the "obligatory role of the endothelium in vasorelaxation by acetylcholine". The other, by Hickey and colleagues, was the first description and characterization of a vasoconstrictor polypeptide produced by endothelial cells in culture. Both of these observations were achieved by the application of bioassay and serendipity played an important role in each of them. They both represent starting points for rapid growth in research activity world-wide leading to the identification of EDRF as nitric oxide, and the polypeptide EDCF as endothelin a few years later. These early observations also raised interest and initiated intensive R&D activity in the pharma industry culminating in the regulatory approval and marketing of novel medicines treating human diseases (48).

51. Prospects for neurodegenerative and psychiatric disorder drug discovery.

The discovery of CNS-active drugs has, to a major extent, resulted from clinical serendipity. Once targets for such compounds were identified, conventional mechanism-based approaches were used to identify new chemical entities for the treatment of neurological and psychiatric disorders. Most of these have, however, failed to display any greater efficacy than existing psychotherapeutics and may, in fact, be less efficacious because of side effect liabilities. Among the reasons for this lack of success in drug discovery include a lack of fundamental knowledge regarding the causes of CNS disorders, the absence of biomarkers for diagnosing and monitoring these conditions, a paucity of animal models that are congruent with the human disease state and the increasing likelihood that CNS conditions are multifactorial in their etiology. These challenges force the inclusion of a Phase IIa proof of concept trial as a component of the drug discovery program. Unlike other therapeutic areas, serendipity is a major factor in the CNS

translational medicine interface requiring a close collaboration between preclinical and clinical scientists trained to appreciate unusual behavioral phenotypes. When combined with conventional target-based drug discovery technologies, this increases the likelihood of identifying truly novel drugs for the treatment of CNS disorders (49).

52. Novel antigen delivery technologies: a review.

Over the past few years, new insights into immunobiology and delivery systems have allowed the development of better vaccines and for a wider range of diseases. Currently available vaccines represent outstanding success story in modern medicine and have had a dramatic effect on morbidity and mortality worldwide. Conventional vaccines have been based on live attenuated, or killed, viruses or bacteria, or recombinant proteins from these organisms. The design of live attenuated vaccines depended to some extent on serendipity and resulted in low success rates. Both live attenuated and killed vaccines require handling of live pathogens and are associated with safety problems. Despite the success of vaccines, there is a clear need for novel antigen delivery technologies to improve vaccine efficacy and safety. Antigen stability, safety, and immunogenicity are the key hurdles in development of novel antigen delivery technologies. Nowadays, various novel drug delivery systems are becoming one of the fastest growing sectors in the pharmaceutical and biotechnological industries. Delivery of vaccines via oral, intranasal, transcutaneous, and intradermal routes will decrease the risk of needle-borne diseases and may eliminate the need for trained personnel and sterile equipment. Currently, various techniques involving DNA vaccines, adjuvants, nanoparticles, liposome, microneedle, and NanoMAP technology are being developed and evaluated (50).

53. From serendipity to therapy.

"My postdoctoral training in the biosynthesis of plant polysaccharides at the University of California, Berkeley, led me, rather improbably, to study mucopolysaccharide storage disorders in the intramural program of the National Institutes of Health (NIH). I have traced the path from studies of mucopolysaccharide turnover in cultured cells to the development of therapy for patients. The key experiment started as an accident, i.e., the mixing of cells of different genotypes, resulting in correction of their biochemical defect. This serendipitous experiment led to identification of the enzyme deficiencies in the Hurler and Hunter syndromes, to an understanding of the biochemistry

of lysosomal enzymes in general, and to the cell biology of receptor-mediated endocytosis and targeting to lysosomes. It paved the way for the development of enzyme replacement therapy with recombinant enzymes. I have also included studies performed after I moved to the University of California, Los Angeles (UCLA), including a recent unexpected finding in a neurodegenerative mucopolysaccharide storage disease, the Sanfilippo syndrome, with implications for therapy" (51).

54. An alternative point of view: getting by with less: what's wrong with perfection?

Predictions about the future impact of technologic and process innovations inspire optimistic visions. Optimism and speculation require a counterweight. Because results often do not turn out as expected, anticipating failure is useful, and anticipating unintended consequences is visionary.

A history of unfulfilled prognostications was explored with the intent of finding something essential to the complexities of medicine. Do missed predictions signal another side to innovation that also helps us uncover new information about our world?

Serendipity is an important theme in medical innovation. There is no reason to think this will change. Things do not necessarily go as planned, but often the results are as important as the original prediction was supposed to be. It will not be clear where we end up until we get there.

Ideal goals are useful but speculative and subjective. There in fact might be several ideals and contingency is important. The detours and incidental stops on the way to an ideal are more fruitful than the goal itself (52).

55. Structure and function of human α -lactalbumin made lethal to tumor cells (HAMLET)-type complexes.

Human α -lactalbumin made lethal to tumor cells (HAMLET) and equine lysozyme with oleic acid (ELOA) are complexes consisting of protein and fatty acid that exhibit cytotoxic activities, drastically differing from the activity of their respective proteinaceous compounds. Since the discovery of HAMLET in the 1990s, a wealth of information has been accumulated, illuminating the structural, functional and therapeutic properties of protein complexes with oleic acid, which is summarized in this review. In vitro, both HAMLET and ELOA are produced by using ion-exchange columns preconditioned with oleic acid. However, the complex of human α -lactalbumin with oleic acid with the antitumor activity of HAMLET was found to be naturally present in the acidic

fraction of human milk, where it was discovered by serendipity. Structural studies have shown that α -lactalbumin in HAMLET and lysozyme in ELOA are partially unfolded, 'molten-globule'-like, thereby rendering the complexes dynamic and in conformational exchange. HAMLET exists in the monomeric form, whereas ELOA mostly exists as oligomers and the fatty acid stoichiometry varies, with HAMLET holding an average of approximately five oleic acid molecules, whereas ELOA contains a considerably larger number (11- 48). Potent tumoricidal activity is found in both HAMLET and ELOA, and HAMLET has also shown strong potential as an antitumor drug in different *in vivo* animal models and clinical studies. The gain of new, beneficial function upon partial protein unfolding and fatty acid binding is a remarkable phenomenon, and may reflect a significant generic route of functional diversification of proteins via varying their conformational states and associated ligands (53).

56. Serendipity and psychopharmacology.

This article describes several examples where the development of drugs and devices for use in psychiatry followed from initial serendipitous observations. The potential psychotropic properties of chlorpromazine (Thorazine®) were first noted in surgical patients when the drug was being investigated as a potentiator of anesthesia. Similar findings were noted with iproniazid (Marsilid®), developed for the treatment of tuberculosis, and the drug was later released for clinical use as an antidepressant agent. The development of meprobamate (Miltown®), an approved treatment for anxiety, evolved from initial efforts to find a chemical that would inhibit the enzymatic destruction of the antibiotic drug penicillin. The psychiatric uses of lamotrigine (Lamictal®) and vagus nerve stimulation were prompted by initial observations that epilepsy patients receiving these treatments had positive mood effects. Nurses should be familiar with the concept of serendipity, as they often are in the best position to observe, record, and report on unexpected clinical effects in patients taking any kind of prescription or nonprescription medication (54).

57. Patent foramen ovale closure and migraine: science and sensibility.

Migraine has been associated with patent foramen ovale (PFO), and PFO closure has become the most high-profile nonpharmacologic invasive therapy recommended for the prevention of recurrent migraine attacks, as well as for preventing further attacks in cryptogenic stroke. The results of Migraine Intervention with STARFlex Technology (MIST), a controversial but important

recent randomized clinical trial (RCT) of PFO closure for migraine, do not support PFO closure for preventing migraine attacks. All patients with migraine, however, do not have a PFO, and the characteristic periodicity and predictability of migraine cannot be explained on the basis of paradoxical embolism through the PFO. Closure of the PFO or atrial septal defect can aggravate migraine suddenly. PFO increases in size with age, but migraine generally subsides with the passage of years. Serendipity does play a role in some medical discoveries, but in the absence of a logically defensible theoretical basis, chance and statistics can both become misleading. With soft end points, RCTs in migraine patients can generate conflicting and irreconcilable data. RCTs cannot supplant or substitute clinical common sense or justify serendipity. Scientific progress mandates that any serendipitous research must ultimately conform to the principles of the basic sciences surrounding the chance discovery. PFO closure for preventing migraine attacks is an unfortunate, but sobering, chapter in the migraine research saga (55).

58. The Charles F. Prentice award lecture 2009: Crystalline lens research and serendipity in science.

Whether it is called serendipity or creativity, the process of scientific discovery is not one that lends itself to advance planning or programming, nor does it lend itself to an emphasis solely on applied research, research with industrial partners, or large teams of researchers because researchers must rely on intuition and the capacity to move quickly in new directions. Studies in my laboratory began with efforts to relate lens embryonic development to lens optical performance in a variety of vertebrate species. The initial direction concerned the optics of the fish eye, a system in which a spherical lens is essentially the only refractive component of the eye and one in which accommodation takes place by means of lens movement. This in turn led to an interest in how amphibious animals cope with the refractive transition that takes place when moving from air to water and vice versa. The development of a super accommodative ability in some diving birds is one adaptation that was explored. These curiosity-driven efforts led in turn to the development of a scanning laser system that provided a tool that can be used to evaluate the process of cataract development, either on the basis of in vivo exposure to chemicals or electromagnetic radiation and subsequent analysis of the excised lens or to the in vitro study of the lens in long-term whole lens culture experiments. The same approach has also been used as an in vitro ocular

toxicology assay to develop sensitive in vitro methods to reduce regulatory dependence on the use of live animals. Finally, these applied directions in turn created new basic knowledge concerning the morphology and physiology of eye tissue organelles, particularly the morphology, distribution, and dynamic properties of the mitochondria found in the lens and in the retinal pigment epithelium (56).

59. Amyloid light chain deposition associated with dermatofibroma: serendipity or association?

Primary cutaneous amyloidosis, also known as nodular amyloidosis, is defined as deposition of amyloid light chain in the skin in the absence of a systemic cause of amyloidosis. Such amyloid is produced by a localized aggregate of clonal plasma cells. In contrast, secondary cutaneous amyloidosis is related to lesions such as squamous cell carcinoma, Bowen disease, basal cell carcinoma, and discoid lupus erythematosus, and has been shown in most cases to be derived from keratin epithelial elements (57).

60. The evolution of antiepileptic drug development and regulation.

The early years of antiepileptic drug development were characterised by observation and serendipity, rather than a rational, targeted approach to drug development. Control of seizures was seen as the primary aim of therapy, with much less focus on safety and tolerability. However, experience with thalidomide in the 1960s brought safety to the fore, resulting in an era of much tighter regulatory control that still persists today. A direct consequence of this was an increased emphasis on the importance of evidence from randomised controlled trials. Despite the continuing reliance on randomised controlled trials for regulatory approval and the formulation of evidence-based guidelines, the modern era has seen an increasing acknowledgment of their limitations and the need for complementary sources of 'real-world' evidence. Such sources include registries and studies that are designed to provide a much broader assessment of a drug's overall effectiveness; for example, by incorporating patient-reported outcomes to assess the effects of treatment on quality of life or functional status. Such changes reflect a more patient-centric approach to treatment, since it is now recognised that epilepsy can only be effectively managed if patients' individual real-life needs are addressed, since a key to successful treatment is long-term compliance. Alongside these changes in approach, the modern era has witnessed important advances in antiepileptic drugs themselves, either through development of novel molecules, or targeted, structural improvements of older agents (58).

61. The ship's log of Ellerbeek: common sense and serendipity in the treatment of scurvy.

In accordance with the usual practice, chief surgeon Joan Ellerbeek recorded his observations during his voyage with the East Indiaman Mars to the Cape of Good Hope in 1776 in a logbook for the Dutch East India Company. During the voyage he was confronted with an increasing number of scurvy patients. Intuitive insight and serendipity led him to try using the seaweed ('Gramen Marinum') which had grown on the ship as an anti-scurvy agent, in the empirical and medical tradition of his time. The results were spectacular. Not only James Lind should therefore be credited with the solution of the problem of scurvy. Many before and after him, including Ellerbeek, also made a contribution (59).

62. A letter from the United States: the fox in our backyard--science, serendipity and surprise.

The story of how Charles Darwin composed *The Origin of Species*, published in November of 1859, has been told many times during the bicentennial of Darwin's birth and the sesquicentennial of the publication of the book. It is a history well known to biologists and historians of science. The heated debate that accompanied the demonstration of natural selection as a mechanism of speciation and continues to the present is surprising. Human beings do not welcome surprise: "the emotion aroused by something unexpected." The history of science and human intellect, however, illustrate the creative stimulus of surprise and serendipity in the development of human knowledge and the evolution of culture. The lives of *Homo sapiens* would not change if our intellect was unable or unwilling to respond to the unexpected and to make connections between surprising and commonplace events. The rich diversity of South American life was surprising to the European travelers of the 18th and 19th centuries: surprising by its beauty and profusion, but also by its similarities to the creatures of Europe and Africa (60).

63. Look but do not fix: the pioneers of interventional cardiovascular radiology.

The extension of endovascular radiological procedures to a one-stop combined investigation and treatment of cardiovascular disease has revolutionized clinical practice. The giants in this respect are Charles Dotter, working from Portland, OR; Mason Sones from the Cleveland Clinic; and Andreas Gruentzig from Zurich and latterly Atlanta, GA. Serendipity and

lateral thinking were pivotal in developing procedures that are now routine (61).

64. Collapsing glomerulopathy: beyond serendipity in mouse genetics.

Clinical correlates suggest that collapsing glomerulopathy results from the pathogenic interaction between patients' intractable genetic susceptibilities and environmental insults. When the environmental insults include a virus that introduces its own pathogenic genes, the interactions become more complex. Chan et al. combine reverse and forward genetic techniques in mice toward understanding this complexity with HIV and identify candidate genetic modifiers of collapsing glomerulopathy (62).

65. Exploiting structural analysis, in silico screening, and serendipity to identify novel inhibitors of drug-resistant falciparum malaria.

Plasmodium falciparum thymidylate synthase-dihydrofolate reductase (TS-DHFR) is an essential enzyme in folate biosynthesis and a major malarial drug target. This bifunctional enzyme thus presents different design approaches for developing novel inhibitors against drug-resistant mutants. We performed a high-throughput in silico screen of a database of diverse, drug-like molecules against a non-active-site pocket of TS-DHFR. The top compounds from this virtual screen were evaluated by in vitro enzymatic and cellular culture studies. Three compounds active to 20 microM IC(50)'s in both wildtype and antifolate-resistant P. falciparum parasites were identified; moreover, no inhibition of human DHFR enzyme was observed, indicating that the inhibitory effects appeared to be parasite-specific. Notably, all three compounds had a biguanide scaffold. However, relative free energy of binding calculations suggested that the compounds might preferentially interact with the active site over the screened non-active-site region. To resolve the two possible modes of binding, co-crystallization studies of the compounds complexed with TS-DHFR enzyme were performed. Surprisingly, the structural analysis revealed that these novel, biguanide compounds do indeed bind at the active site of DHFR and additionally revealed the molecular basis by which they overcome drug resistance. To our knowledge, these are the first co-crystal structures of novel, biguanide, non-WR99210 compounds that are active against folate-resistant malaria parasites in cell culture (63).

66. Bacterial toxins as immunomodulators.

Bacterial toxins are the causative agent at pathology in a variety of diseases. Although not always the primary target of these toxins, many have been

shown to have potent immunomodulatory effects, for example, inducing immune responses to co-administered antigens and suppressing activation of immune cells. These abilities of bacterial toxins can be harnessed and used in a therapeutic manner, such as in vaccination or the treatment of autoimmune diseases. Furthermore, the ability of toxins to gain entry to cells can be used in novel bacterial toxin based immuno-therapies in order to deliver antigens into MHC Class I processing pathways. Whether the immunomodulatory properties of these toxins arose in order to enhance bacterial survival within hosts, to aid spread within the population or is pure serendipity, it is interesting to think that these same toxins potentially hold the key to preventing or treating human disease (64).

67. Historical perspectives in critical care medicine: blood transfusion, intravenous fluids, inotropes/vasopressors, and antibiotics.

Significant progress in critical care medicine has been the result of tireless observation, dedicated research, and well-timed serendipity. This article provides a historical perspective for four meaningful therapies in critical care medicine: blood transfusion, fluid resuscitation, vasopressor/inotropic support, and antibiotics. For each therapy, key discoveries and events that have shaped medical history and helped define current practice are discussed. Prominent medical and social pressures that have catalyzed research and innovation in each domain are also addressed, as well as current and future challenges (65).

68. Living in the electronic age: musings on nearly two decades in Cyberspace.

My journey through Cyberspace began about 20 years ago with an introduction to e-mail. A few years later, I had the good fortune of working with artificial intelligence engineers who were developing information retrieval techniques and expert systems. By serendipity this led to an early introduction to the World Wide Web (www) and the use of Web browsers as tools for gathering information, long before the Internet became commercialized. Internet content and form are now so omnipresent that they have affected our language in both amusing and utilitarian ways. We are entering an era where social networking, from personal to professional lives, is potentially a vibrant new direction for the Internet. Future articles for this feature will explore how to maximize the utility of the Internet (66).

69. My journey to the ants.

In this paper, I review the strange, unplanned and unexpected journey I have had with *Solenopsis invicta*, the imported fire ant. Through serendipity, good fortune and repeated invenomation, I have come to count as collaborators a number of entomologists, toxicologists, allergists and immunologists who have guided me on this journey to the ants. We now understand the mechanisms for the cutaneous reactions experienced by 50% of the exposed population stung per year, as well as the immunologic and toxicologic properties of the ants unique venom. Allergen immunotherapy to fire ant extracts has been demonstrated to protect patients from repeat anaphylaxis. Methods have been developed to prevent and treat massive sting attacks on frail elders, including those in residential and medical facilities. The potential beneficial effects of venom components are under investigation. And yes, the journey and the stings continue (67).

70. Developing drugs that can cross the blood-brain barrier: applications to Alzheimer's disease.

Development of therapeutics for the central nervous system is one of the most challenging areas in drug development. This is primarily because, in addition to all of the other complications one faces in developing new drugs targeting peripheral sites, one must also negotiate the blood-brain barrier (BBB). There are dozens of strategies to overcome the obstacle of the BBB, but many of these are bound to fail, barring extreme serendipity, because they are based on an inaccurate or incomplete picture of the BBB. This article therefore starts with a brief review of the BBB as it pertains to drug development. It then examines some examples of the delivery of drugs to the central nervous system that are relevant to Alzheimer's disease, placing emphasis on peptides, antibodies, and antisense oligonucleotides (68).

71. Ruggero Oddi: 120 years after the description of the eponymous sphincter: a story to be remembered.

This article presents a short account of theories, methods, and experimental data formulated and carried out 120 years ago, by Ruggero Oddi, then a 4th-year student in medicine, about the identification of the common bile duct sphincter. A historical picture emerges which leads us to think that Oddi not only discovered the bile duct sphincter, but also described bile duct dilation after cholecystectomy and performed biliary manometry for the first time. The role of serendipity and the almost unknown contribution of Arturo Marcacci, Oddi's "maestro" are also mentioned (69).

72. Diagnosis by serendipity: Cushing syndrome attributable to cortisol-producing adrenal adenoma as the initial manifestation of multiple endocrine neoplasia type 1 due to a rare splicing site MEN1 gene mutation.

To report a case that highlights the potential for Cushing syndrome to be the first manifestation of multiple endocrine neoplasia type 1 (MEN 1) syndrome and to describe the rare underlying genetic mutation and the heterogeneous manifestations of the syndrome within the same family.

We present a case report including biochemical and radiologic findings, review family data, and discuss the results of genetic analyses.

A 16-year-old girl who was not known to have any medical illness and had no known family history of MEN 1 syndrome presented with Cushing syndrome attributable to a cortisol-producing adrenal adenoma. During her evaluation, she was found to have primary hyperparathyroidism and a pituitary microprolactinoma. These findings raised the possibility of MEN 1 syndrome. She did not have clinical, biochemical, or radiologic evidence of islet cell pancreatic tumors. Family screening showed that her father had evidence of primary hyperparathyroidism, mild hyperprolactinemia, normal findings on magnetic resonance imaging of the pituitary, and a 1.2-cm nodule in the tail of the pancreas in conjunction with slight elevation of serum insulin and normal gastrin levels. The patient's 5 siblings had evidence of primary hyperparathyroidism, and 2 of them also had mild hyperprolactinemia. Genetic screening confirmed the presence of a MEN1 gene missense G to A mutation in the patient, her father, and her siblings at the splicing site of intron 6 (IVS6+1G>A). This mutation leads to frameshift and truncation of the MEN1 gene.

In MEN 1, Cushing syndrome is an extremely rare and usually late manifestation. Most cases are due to corticotropin-producing pituitary adenomas. Although Cushing syndrome generally develops years after the more typical manifestations of MEN 1 appear, it may be the primary manifestation of MEN 1 syndrome. There is considerable heterogeneity in the manifestations of MEN 1, even within a family having the same genetic mutation (70).

73. Major depression: emerging therapeutics.

The first effective antidepressants, monoamine oxidase inhibitors and tricyclic antidepressants, were identified 50 years ago, largely through serendipity.

These medications were found to improve mood in a little more than half of depressed patients after a few weeks of chronic use. Almost all antidepressants prescribed today were developed through minor modifications of these original antidepressants and, like monoamine oxidase inhibitors and tricyclic antidepressants, act primarily through monoaminergic mechanisms. Although there have been improvements in side-effect profiles and overdose toxicity, these newer medications have not provided substantial advances in the efficacy and speed of the antidepressant effect for patients. Over the last 2 decades, our understanding of the neurobiology underlying depression has expanded exponentially. Given this expansion, we may be nearing an inflection point in antidepressant drug development, at which useful medicines will be designed through a rational understanding of the biological systems (71).

74. The discovery of biological enantioselectivity: Louis Pasteur and the fermentation of tartaric acid, 1857--a review and analysis 150 yr later.

Nearly a decade after discovering molecular chirality in 1848, Louis Pasteur changed research direction and began investigating fermentations. Conflicting explanations have been given for this switch to microbiology, but the evidence strongly suggests that Pasteur's appointment in 1854 to the University of Lille--an agricultural-industrial region where fermentation-based manufacturing was of great importance--and an appeal for help in 1856 by a local manufacturer experiencing problems in his beetroot-fermentation-based alcohol production played a significant role. Thus began, in late 1856, Pasteur's pioneering studies of lactic and alcoholic fermentations. In 1857, reportedly as a result of a laboratory mishap, he found that in incubations of ammonium (+/-)-tartrate with unidentified microorganisms (+)-tartaric acid was consumed with considerable preference over (-)-tartaric acid. In 1860, he demonstrated a similar enantioselectivity in the metabolism of tartaric acid by *Penicillium glaucum*, a common mold. Chance likely played a significant role both in Pasteur's shift to microbiology and his discovery of enantioselective tartrate fermentations, but he rejected pure serendipity as a significant factor in experimental science and in his own career. Pasteur's milestone discovery of biological enantioselectivity began the process that in the long run established the fundamental importance of molecular chirality in biology (72).

75. Canine cytogenetics--from band to basepair

Humans and dogs have coexisted for thousands of years, during which time we have developed a unique bond, centered on companionship. Along the

way, we have developed purebred dog breeds in a manner that has resulted unfortunately in many of them being affected by serious genetic disorders, including cancers. With serendipity and irony the unique genetic architecture of the 21st century genome of Man's best friend may ultimately provide many of the keys to unlock some of nature's most intriguing biological puzzles. Canine cytogenetics has advanced significantly over the past 10 years, spurred on largely by the surge of interest in the dog as a biomedical model for genetic disease and the availability of advanced genomics resources. As such the role of canine cytogenetics has moved rapidly from one that served initially to define the gross genomic organization of the canine genome and provide a reliable means to determine the chromosomal location of individual genes, to one that enabled the assembled sequence of the canine genome to be anchored to the karyotype. Canine cytogenetics now presents the biomedical research community with a means to assist in our search for a greater understanding of how genome architectures altered during speciation and in our search for genes associated with cancers that affect both dogs and humans. The cytogenetics 'toolbox' for the dog is now loaded (73).

76. Never resting brain: simultaneous representation of two alpha related processes in humans.

Brain activity is continuously modulated, even at "rest". The alpha rhythm (8-12 Hz) has been known as the hallmark of the brain's idle-state. However, it is still debated if the alpha rhythm reflects synchronization in a distributed network or focal generator and whether it occurs spontaneously or is driven by a stimulus. This EEG/fMRI study aimed to explore the source of alpha modulations and their distribution in the resting brain. By serendipity, while computing the individually defined power modulations of the alpha-band, two simultaneously occurring components of these modulations were found. An 'induced alpha' that was correlated with the paradigm (eyes open/ eyes closed), and a 'spontaneous alpha' that was on-going and unrelated to the paradigm. These alpha components when used as regressors for BOLD activation revealed two segregated activation maps: the 'induced map' included left lateral temporal cortical regions and the hippocampus; the 'spontaneous map' included prefrontal cortical regions and the thalamus. Our combined fMRI/EEG approach allowed to computationally untangle two parallel patterns of alpha modulations and underpin their anatomical basis in the human brain. These findings suggest that the human alpha rhythm represents at least two simultaneously occurring processes which characterize the 'resting brain'; one is related to expected change in sensory

information, while the other is endogenous and independent of stimulus change (74).

77. Science and serendipity.

Good science demands independent replication of new ideas and results and abandonment of accepted theories in light of more reliable evidence. Failure to comply leads to damaging bad science, as with the falsely claimed association between measles, mumps and rubella vaccination and autism. Progress of good science also often requires serendipity, 'making discoveries by accident and sagacity of things not sought'. Work on the pentraxin proteins, C-reactive protein (CRP) and serum amyloid P component (SAP), and on amyloidosis, has benefited from abundant serendipity, leading to routine clinical use of CRP measurements, the invention of SAP scintigraphy for amyloidosis, the establishment of the NHS National Amyloidosis Centre providing superior patient care, and latterly the invention of a novel pharmacological mechanism for therapeutic depletion of pathogenic proteins. New drugs using this mechanism are in development for amyloidosis and cardiovascular disease and potentially also Alzheimer's disease, type II diabetes and other tissue damaging conditions (75).

78. Sensitivity of immunochemical fecal occult blood test to small colorectal adenomas.

Although the immunochemical fecal occult blood test (FOBT) is reportedly more sensitive to large adenomas or colorectal cancer (CRC) than the guaiac-based FOBT, the sensitivity of the immunochemical FOBT to small adenomas has scarcely been reported. Previous reports have indicated that the guaiac-based FOBT can detect small adenomas only by serendipity.

To investigate the sensitivity of immunochemical FOBT to small adenomas using a large-scale cohort.

We analyzed 21,805 consecutively enrolled asymptomatic persons who underwent colonoscopy and immunochemical FOBT.

The sensitivity to adenomas ≤ 9 mm was significantly higher than the false-positive rate as revealed by analysis of all eligible subjects (7.0% vs 4.5%, $P < 0.001$). In men, the sensitivity was superior to the false-positive rate and increased with age (<50 yr 6.1% and >60 yr 11.3%). On the other hand, the sensitivity in women was not significantly different from the false-positive rate in any generation (5.1% vs 4.7% for all eligible women, $P = 0.72$).

Immunochemical FOBT detected a small percentage of small adenomas in men at a rate that is significantly higher than the false-positive rate. Studies comparing the guaiac and immunochemical FOBTs using the end point of CRC-related death are expected (76).

79. FTY720 story. Its discovery and the following accelerated development of sphingosine 1-phosphate receptor agonists as immunomodulators based on reverse pharmacology.

Fingolimod (FTY720) is the first of a novel class: sphingosine 1-phosphate (S1P) receptor modulator and is currently in phase 3 clinical trials for multiple sclerosis (MS). FTY720 was first synthesized in 1992 by chemical modification of an immunosuppressive natural product, ISP-I (myriocin). ISP-I was isolated from the culture broth of *Isaria sinclairii*, a type of vegetative wasp that was an 'eternal youth' nostrum in traditional Chinese medicine. ISP-I is an amino acid having three successive asymmetric centers and some functionalities. We simplified the structure drastically to find a nonchiral symmetric 2-substituted-2-aminopropane-1,3-diol framework for an in vivo immunosuppressive activity (inhibition of rat skin allograft rejection test or prolonging effect on rat skin allograft survival) and finally discovered FTY720. During the course of the lead optimization process, we encountered an unexpected dramatic change of the mechanism of action with an in vivo output unchanged. Since it proved that FTY720 did not inhibit serine palmitoyltransferase that is the target enzyme of ISP-I, reverse pharmacological approaches have been performed to elucidate that FTY720 is mainly phosphorylated by sphingosine kinase 2 in vivo and the phosphorylated drug acts as a potent agonist of four of the five G protein coupled receptors for S1P: S1P(1), S1P(3), S1P(4) and S1P(5). Evidence has accumulated that immunomodulation by FTY720-P is based on agonism at the S1P(1) receptor. Medicinal chemistry targeting S1P(1) receptor agonists is currently in progress. The FTY720 story provides a methodology where in vivo screens rather than in vitro screens play important roles in the lead optimization. Unlike recent drug discovery methodologies, such a strategy as adopted by the FTY720 program would more likely meet serendipity (77).

80. From serendipity to technology: use of a web-based information and booking system to improve clinical attachments at a district general hospital.

Clinical attachments form a vital part of the learning experience for medical students but may vary in educational value. This paper describes a project

intended to improve the quality of attachments at a District General Hospital in Devon, UK after negative feedback was received from students.

To improve educational quality by providing information and choice for students.

The intervention was to set up a web-based system that allowed students to view before arrival all educational opportunities available, not only in the hospital but in the surrounding district. Students were contacted by email 2 weeks before their attachment and were then able to construct their own timetable from the menu of opportunities available.

The system was popular with students, recruited new providers of learning opportunities and also integrated learning across primary and secondary care.

The intervention encouraged a sense of ownership of the learning experience as well as maximising the use of available learning resources (78).

81. Current trends in migraine prophylaxis.

A variety of drugs from diverse pharmacological classes are in use for migraine prevention. Traditionally, they have been discovered by serendipity. Examples include beta-adrenergic blockers, anticonvulsants, tricyclic antidepressants, and serotonin receptor antagonists. The mechanisms of action of migraine preventive drugs are multiple but it is postulated that they converge on two targets: (1) inhibition of cortical excitation; (2) restoring nociceptive dysmodulation. The antiepileptic drugs (e.g., topiramate, valproate, gabapentin), calcium channel blockers such as verapamil, and inhibitors of cortical spreading depression are some examples of drugs that reduce neuronal hyperexcitability. On the other hand, modulators of the serotonergic and adrenergic systems and cholinergic enhancing drugs may restore descending nociceptive inhibition and play a role in migraine prevention. To date, Level 1 evidence and clinical experience favor the use of the antidepressant amitriptyline, the anticonvulsants divalproex and topiramate, and the beta-adrenergic blockers propranolol, timolol and metoprolol as first line migraine preventive drugs. The evidence for others (e.g., verapamil) is not as strong. Migraine preventive drugs have varying degrees of adverse effects, some of which could be limiting, and their efficacy should be balanced with their risks of adverse effects, patients' expectations and desires, and compliance. It is hoped that future migraine preventive drugs target migraine mechanisms more specifically, which could well enhance the therapeutic index (79).

82. Human heme oxygenase-1 deficiency: a lesson on serendipity in the discovery of the novel disease.

The first case of human heme oxygenase (HO)-1 deficiency was reported by Yachie et al. at our laboratory in the Department of Pediatrics, Angiogenesis and Vascular Development, Kanazawa University Graduate School of Medical Science, in 1999. In the present paper I would like to review this novel disease. Our studies into HO-1 deficiency were called by us 'Kanazawa version Project X'. From the story of our successful discovery we have learned that serendipity is a very important spiritual factor. Serendipity is the making of fortunate and unexpected discoveries by chance (from its possession by the heroes in the Persian fairy tale The Three Princes of Serendip) (80).

83. Highlights in experimental therapeutics.

The past two decades have seen a dramatic change in cancer treatment paradigms. Anticancer agents are no longer being developed based on empiricism and serendipity, but are now being aimed to inhibit a validated target that is relatively specific for tumours rather than normal cells. The vast majority of cancers arise from multiple genetic lesions; thus, sophisticated drug cocktails, or single drugs acting on multiple downstream targets will be needed for successful cancer therapy. Three emerging concepts that are addressing these therapeutic needs and that are key to blocking steps in tumorigenesis will be highlighted in this review: (a) attacking cancer cell immortality by targeting the telomere/telomerase complex; (b) targeting oncogene activation by inhibiting the molecular chaperone Hsp90; and (c) stabilizing tumour suppressor proteins by modulating the ubiquitin-proteasome system (81).

84. Biology of RANK, RANKL, and osteoprotegerin.

The discovery of the receptor activator of nuclear factor-kappaB ligand (RANKL)/RANK/osteoprotegerin (OPG) system and its role in the regulation of bone resorption exemplifies how both serendipity and a logic-based approach can identify factors that regulate cell function. Before this discovery in the mid to late 1990s, it had long been recognized that osteoclast formation was regulated by factors expressed by osteoblast/stromal cells, but it had not been anticipated that members of the tumor necrosis factor superfamily of ligands and receptors would be involved or that the factors involved would have extensive functions beyond bone remodeling. RANKL/RANK signaling

regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling and in a variety of pathologic conditions. OPG protects the skeleton from excessive bone resorption by binding to RANKL and preventing it from binding to its receptor, RANK. Thus, RANKL/OPG ratio is an important determinant of bone mass and skeletal integrity. Genetic studies in mice indicate that RANKL/RANK signaling is also required for lymph node formation and mammary gland lactational hyperplasia, and that OPG also protects arteries from medial calcification. Thus, these tumor necrosis factor superfamily members have important functions outside bone. Although our understanding of the mechanisms whereby they regulate osteoclast formation has advanced rapidly during the past 10 years, many questions remain about their roles in health and disease (82).

85. Remembrance of weaning past: the seminal papers.

The approach to ventilator weaning has changed considerably over the past 30 years. Change has resulted from research in three areas: pathophysiology, weaning-predictor testing, and weaning techniques. Physiology research illuminated the mechanisms of weaning failure. It also uncovered markers of weaning success. Through more reliable prediction, patients whose weaning would have been tedious in the 1970s are now weaned more rapidly. The weaning story offers several lessons in metascience: importance of creativity, the asking of heretical questions, serendipity, mental-set psychology, cross-fertilization, and the hazards of precocity. Weaning research also illustrates how Kuhnian normal (me-too) science dominates any field. Making the next quantum leap in weaning will depend on spending less time on normal science and more on the raising (and testing) of maverick ideas (83).

86. Reflections: the hospitalist movement a decade later.

August 2006 marks the 10th anniversary of the publication of an article in the New England Journal of Medicine in which Lee Goldman and I coined the term hospitalist—an event that many people characterize as the start of the hospitalist movement in the United States. The present article describes the history of those early days, highlighting some of the choices the field's initial leaders made to nurture the new specialty. In retrospect, although there were many examples of fortunate serendipity, there were also several key strategic choices, including the focus on gathering research data to demonstrate the value of the field to external stakeholders; the forceful rejection of mandatory

hospitalist systems, particularly those promoted by managed care organizations; and the purposeful linking of our new field to the burgeoning movements to improve quality and patient safety in hospitals. Most of all, the field's spectacular growth and successes can be attributed to the daily work of thousands of hospitalists in clinical care, education, research, and systems improvement. These individuals have given life to our theoretical notion a decade ago that a new model for inpatient care would improve the American health care system and the care of inpatients (84).

87. Overcoming the force and power of immunity: a history of immunosuppression in kidney transplantation.

Immunosuppression for organ transplantation is a modern concept. The earliest reports of organ replacement have their roots in mythology and human fantasy. The primacy of overcoming the immunologic barrier for successful transplantation of organs has been influenced by geopolitical conflict, unorthodox ideas, application of knowledge across medical disciplines, and serendipity. The earliest form of chemical immunosuppression had its origin in chemical gas in warfare. Further developments in immunology, cancer therapy and biochemistry helped shape the intellectual basis for the introduction of chemical immunosuppression (85).

88. Paul Ehrlich's "Mastzellen"--from aniline dyes to DNA chip arrays: a historical review of developments in mast cell research.

It has been more than a century since the discovery of the mast cell by the genius and tenacity of Paul Ehrlich, who described this cell when he was a medical student. One cannot deny that this discovery also coincides with the golden age of immunology. The discovery of this important cell type in immunological history was no serendipity: it was a result of Ehrlich's prodigious laboratory talent and his ability to combine intuition and deduction despite the limited resources of his times. Since then, we have learned much more about the immune response, immunoglobulin E, and the development and function of mast cells in various pathological states. What follows is a review of Paul Ehrlich's discovery of the mast cell (mästzellen) and a chronological review of subsequent developments in mast cell research, including the recent use of proteomics and genomics to understand mast cell biology (86).

89. Christine McGuire: at the heart of the maverick measurement maven.

In this article, part of the Exemplar series in *Advances in Health Sciences Education*, we profile the career of Christine McGuire, and capture her perspectives on the status of medical education practice and research. Her career was prototypical of other exemplars in the series--a pathway characterized by serendipity. As an exemplar, her contributions of leadership, scholarship, and innovations have changed the face of medical education. We describe our methods of data collection--literature reviews and in-depth interviews. We provide a portrayal of her career and accomplishments. Finally, we characterize her perspectives on medical education, including her views of significant innovations, contributions of professional educators, lessons learned, and needed future efforts (87).

90. Serendipitous insights involving nonhuman primates.

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 (88).

91. Observation and cogitation: how serendipity provides the building blocks of scientific discovery.

The identification of serendipitous findings in field-based animal research is challenging in part because investigators are reluctant to declare a discovery

accidental. Investigators recognize that many factors must be considered. For example, the impact of using carefully ordered observational search patterns in ecologic, pathologic, and epidemiologic investigations could result in findings being categorized as "sought" versus "unsought." Team collaborations are common in these types of investigations and have advantages related to the application of multiple paradigms, paradigm mixing, and paradigm shifting. This approach reduces the perception of serendipity. Issues of search image refinement and the co-discovery of sought and unsought discoveries additionally cloud the identification of a truly serendipitous finding. Nevertheless, basic curiosity and observation are necessary precursors to scientific discovery. It should be recognized that serendipitous discoveries are of significant value in the advancement of science and often present the foundation for important intellectual leaps of understanding (89).

92. Clinical PD/PDT in North America: An historical review.

The healing properties of light have been appreciated for thousands of years. However, the harnessing of light energy to create a rigorous and reliable means to diagnose and treat human disease is only a relatively recent phenomenon. Despite outstanding results from ancient history and subsequent reemergence and refinement of this knowledge over the last 100 years, it took again the hand of serendipity to open the modern age of Photodiagnosis and Photodynamic Therapy. Based on the prescience and perseverance of a handful, the under appreciated observations of tumor fluorescence and photodynamic action have been brought to a worldwide audience (90).

93. Women, pregnancy and serendipity: a personal story about the discovery of HLA.

The discovery of HLA was an adventure in many ways very much like the discovery of a new continent with many people entering it from different angles. This has been a truly global effort with laboratories from all over the world voluntarily collaborating. The picture that finally emerged of a highly complex genetic system and its role in biology and medicine was and is fascinating. I have been involved from almost the beginning in the HLA story and have watched--often from nearby--the breakthroughs insights that opened new aspects of HLA. A discovery is not a gradual process, but one, which goes with jumps and laps. I will therefore not give a chronological summing up

what happened, but limit myself to turning points, the sudden flashes of insight, which made working in HLA so exciting and rewarding (91).

94. The short story of HLA and its methods.

During the past 40 years, typing for the human leukocyte antigens (HLA) was done using serological techniques. Several improvements were achieved as to the efficiency and reliability of these techniques. One of the major drawbacks of serology, however, is the need of viable cells. Especially blood cells drawn from deceased donors, as are the usual source for typing of corneal donors, may have a grossly impaired viability and a reduced expression of antigens on their cell surface. This makes serological typing difficult and liable to errors. In the mid-1980s, molecular typing was first introduced in many laboratories. This first period dealt with the so-called restriction fragment length polymorphism method, a tedious method not suited for prospective typing. Only with the introduction of the polymerase chain reaction was the suitability of molecular techniques with respect to prospective typing achieved.

International workshops and the effort of many laboratories led to a standardization of the methods. External proficiency testing exercises on transplantation relevant procedures in the laboratories affiliated to transplantation centers and the introduction of an accreditation system in the USA and in Europe increased significantly the reliability of all relevant immunogenetical testing.

To date, patients and prospective organ and tissue donors are typed in addition to serology also with molecular methods. Using these techniques, the reliability and reproducibility of HLA typing have reached levels of more than 98%. Even 8-day-old peripheral blood samples can now be typed routinely with these methods, formerly impossible by serology.

The laboratories affiliated to the transplantation centers are ready for high reliability testing of all HLA markers required by the clinic according to the results of controlled clinical long-term follow-up studies (92).

95. Clinical comparability of marketed formulations of botulinum toxin.

The majority of pharmaceutical products are patented in early phases of their discovery to preclude competition by similar products. Due to unusual circumstances (botulinum toxin is an unpatentable natural product and it is considered to be a biological weapon), technology know-how for botulinum

toxin production was classified rather than available in the scientific community. Botulinum toxin type A was marketed in two pharmaceutical distinct formulations from competitor companies. Serendipity proved that the two formulations were not equipotent in terms of mouse units. From a regulatory point of view, differences in potency of distinct formulations are not a matter of concern because each formulation is licensed based on its own set of data. As far as the data in each case is sufficient to prove that a particular formulation is safe and efficacious at its defined dosage, a license for use can be granted. On the other hand, generation of data on comparability is the only way that clinicians and managers can ascertain which product (formulation, serotype) is most cost-effectiveness and to determine whether there are relevant differences in their safety profiles. The results of the systematic review of head-to-head randomised trials comparing BOTOX to Dysport suggest that the two formulations are not bioequivalent whatever the dose relationship. Data on comparative immunogenicity are not available. The indirect comparison of the results obtained in randomised clinical trials comparing BOTOX to placebo and Dysport to placebo support that intrinsic differences are present in the two products. It is concluded that comparative economic evaluations of different botulinum toxin formulations should move away from cost-minimization approaches based on the presumption of bioequivalence and move toward cost-effectiveness or cost-utility models (93).

96. Tumor intracellular redox status and drug resistance--serendipity or a causal relationship?

Reducing tumor load by therapeutic induction of cell death in the transformed phenotype is the desirable goal of most chemotherapeutic regimens. Despite the tremendous strides made in our understanding of mechanisms that endow tumor cells with the ability to evade execution signals, development of chemoresistance is still a major obstacle in the successful management of the disease. A host of factors have been implicated in the acquisition of the resistant phenotype, such as activation of drug efflux pumps, overexpression of proteins that inhibit cell death, absence of critical members of the death circuitry, and selective loss of cell cycle checkpoints. Consequently, it is now well established that the process of carcinogenesis is not only a result of an increase in cells' proliferative capacity, but a product of increased proliferation and defective or diminished cell death signaling. To that end, one of the critical determinants of cellular response to exogenous stimuli is the cellular

redox status. Intracellular generation of reactive oxygen species (ROS) is tightly regulated by the intrinsic anti-oxidant defense systems. Despite the conventional dogma that ROS are harmful to the cell, experimental evidence over the last decade or so bear witness to the fact that ROS also play an important role as signaling molecules in diverse physiological processes. Indeed, low levels of intracellular ROS have been linked to cellular proliferation and cell cycle progression, which provides an explanation for the pro-oxidant state invariably associated with the transformed phenotype. Coupled to that are recent observations implicating pro-oxidant intracellular milieu in tumor cells' resistance to cell death signals delivered through the cell surface receptor or upon exposure to chemotherapeutic drugs. These studies provide convincing evidence to support a direct or indirect role for intracellular superoxide anion in creating an intracellular milieu non-permissive for cell death execution. Thus a novel approach to enhancing tumor cell sensitivity to chemotherapy-induced cell death would be to favourably tailor the cytosolic milieu to allow efficient apoptotic execution (94).

97. Advancing the treatment of mood and anxiety disorders: the first 10 years' experience with paroxetine.

The last half of the 20th century witnessed remarkable advances in the field of psychiatry that began with serendipity and were realized through the combined efforts of astute clinical observation, scientific investigation, and patient advocacy. The modern era of psychopharmacology of mood disorders began in the late 1940s with John Cade's discovery of the mood-stabilizing properties of lithium.¹ Less than 5 years later came the unexpected observation of elevated mood and activation among patients on a tuberculosis ward who were treated with the antitubercular agent, iproniazid. Subsequent clinical trials led to the widespread, but short-lived, use of iproniazid for treatment of depression in 1957 and demonstration of its monoamine oxidase inhibitor properties (95).

98. The molecular turn in psychiatry: a philosophical analysis.

Biological psychiatry has been dominated by a psychopharmacologically-driven neurotransmitter dysfunction paradigm. The objective of this paper is to explore a reductionist assumption underlying this paradigm, and to suggest an improvement on it. The methods used are conceptual analysis with a comparative approach, particularly using illustrations from the history of both biological psychiatry and molecular biology. The results are that complete reduction to physicochemical explanations is not fruitful, at least in the initial

stages of research in the medical and life sciences, and that an appropriate (non-reducible) integrative principle--addressing a property of the whole system under study--is required for each domain of research. This is illustrated in Pauling's use of a topological integrative principle for the discovery of the functioning of proteins and in Watson and Crick's use of the notion of a genetic code as an integrative principle for the discovery of the structure of genes. The neurotransmitter dysfunction paradigm addresses single molecules and their neural pathways, yet their interactions within the CNS as a whole seem most pertinent to mental disorders such as schizophrenia. The lack within biological psychiatry of an integrative principle addressing a property of the CNS as a whole may be responsible for the empirical failure of orthomolecular psychiatry, as well as for the central role that serendipity has played in the study of mental disorders, which is dominated by the neurotransmitter paradigm. The conclusion is that research in biological psychiatry may benefit from using, at least initially, some integrative principle(s) addressing a property of the CNS as a whole, such as connectionism or a hierarchical notion (96).

99. Immunotherapy for psoriasis: from serendipity to selectivity.

The opening years of this millennium saw a substantial increase in the number of pharmaceutical and biotechnology companies developing systemic therapies for psoriasis. These companies have focused on T-cells and cytokines as attractive, possibly lucrative, targets. This endeavour is the logical extension of observations, both serendipitous and mechanistic, made 15–20 years ago. Before 1980 most dermatologists viewed psoriasis primarily as a disease of epidermal keratinocyte hyper-proliferation, and its attendant cutaneous inflammation as a secondary feature (97).

100. Directions of drug discovery in osteoporosis.

Osteoporosis is a condition of increasing importance and prevalence in all parts of the world and particularly in Asia. Recent advances have led to the introduction of effective drugs that decrease bone resorption and stabilize bone mass. However, these drugs have been identified by serendipity rather than rational drug design and are not ideal because of limited bioavailability, mode of administration, or other unwanted effects. There is still a place for even more suitable and effective resorption inhibitors than those currently available. The more compelling need in this field is an acceptable drug that is anabolic for bone, that safely and acceptably increases bone mass and

improves the disturbances in bone microarchitecture that characterize established and advanced osteoporosis (98).

101. Neonatal lead poisoning from maternal pica behavior during pregnancy.

Lead toxicity has gained increasing attention in the public media because of its ubiquitous distribution in the environment and the potentially serious medical complications that it can induce, particularly in children. We present a case of an asymptomatic Hispanic woman who exhibited a unique form of pica during her pregnancy. By serendipity, she agreed to enroll into a lead screening study at our medical center when she presented to deliver her child. Her blood lead level was 119.4 microg/dL at delivery, and simultaneous measurement of the neonate's cord blood lead level was 113.6 microg/dL. The infant underwent an exchange transfusion, and the mother was treated with oral 2,3-dimercaptosuccinic acid. Both demonstrated dramatic biochemical improvement (99).

102. The interplay of biology and technology.

Technologies for biological research arise in multiple ways- through serendipity, through inspired insights, and through incremental advances-and they are tightly coupled to progress in engineering. Underlying the complex dynamics of technology and biology are the different motivations of those who work in the two realms. Consideration of how methodologies emerge has implications for the planning of interdisciplinary centers and the training of the next generation of scientists (100).

103. Partners: serendipity in arbovirus research.

A review of 60 years of research on mosquito-borne arboviruses in the Western U.S.A. revealed a number of instances when serendipity influenced the development of new concepts or novel approaches to solve ecological or epidemiological problems. Eight such events were selected as examples. The need for effective mosquito traps to collect live mosquitoes to be tested for virus infection posed design problems and also led to the use of CO₂ (dry ice) as a mosquito attractant. This research also led to identification of *Culex tarsalis* as a primary target for vector control programs in the western U.S.A. Attendance at a movie led to development of fluorescent dusts to mark mosquitoes for studies of their numbers, life tables and movements. Knowledge of vector-virus associations was used to influence state legislative action to provide funding for vector control and further discovery of vector-

virus associations. Derivation of the term "Arbovirus" started as laboratory jargon and evolved into being the classification for over 500 vector-borne viruses. Sociobiological changes resulting from the use of television and air conditioning fortuitously decreased exposure of California residents to vector attack. These two changes were introduced into households in California in the early 1950s. The prime time when *C. tarsalis*, the primary vector of encephalitis, bites people is around sundown which also is primetime for television watching. These sociological changes are a valuable adjunct to vector control programs (101).

104. Surgical dogmas throughout history.

This article is a historical analysis of the role of dogmas and dogmatic thinking in surgery from the great pioneers and teachers of surgery of a hundred years ago to the present time. Medical knowledge applied schematically creates security and may benefit many patients, but when simplification and standardization degenerates into rigid dogma, creative thinking will be obstructed and the development of innovative concepts becomes difficult. In the old times of the 19th and early years of the 20th century, dogmas usually originated from the teaching of great and prestigious pioneers of surgery. Nowadays, dogmatic thinking may come as practice guidelines, protocols of consensus conferences and even from the interpretation of the results of prospective randomized studies. The author illustrates these thoughts by a number of examples taken from the history of surgery over the last one hundred years: The controversy between Sauerbruch's (under) pressurized chamber and the concept of intratracheal positive pressure ventilation and its influence on the development of thoracic surgery during the first half of the 20th century, the role of serendipity and undogmatic thinking in the development of damage control surgery towards the end of the 20th century, the fascinating history of two operations which kept their position as gold standard for almost a century, i.e. Halsted's radical mastectomy for breast cancer and the Miles operation for cancer of the rectum (102).

105. Poisoning the spindle: serendipity and discovery of the anti-tumor properties of the Vinca alkaloids.

In 1995, Canadian scientists Robert Noble and Charles Beer were inducted into the Canadian Medical Hall of Fame for their 1950s "discovery" of Vinblastine. Their "chance" finding of an anticancer drug in the leaves of the periwinkle plant (*Vinca rosea*, Linn.), is used to explore the historical issue of discovery, accidental discovery, and priority. The elements of the discovery

are reconstructed through the oral testimony of key players and their published and unpublished records. Several "unsung heroes" played key roles in this project and reasons for their relative invisibility will be presented. Special attention is paid to the relationship between the small Canadian academic group working at UWO and the large pharmaceutical company (Eli Lilly) engaged in similar research at the same time (103).

106. Serendipity and the development of heparin and carbon surfaces.

In the early 1960s, bileaflet valves fabricated with polymer housings routinely thrombosed within a few hours after implantation in the canine heart. In a serendipitous series of events, the authors found a way to bond heparin to these bileaflet valves using a coating of graphite-carbon and benzalkonium chloride. Over the ensuing 30 years, improved heparin coatings have been developed by other investigators for bonding to various biomedical devices; currently, about 25% of oxygenators used in this country utilize heparin coatings to minimize surface activation of clotting factors. Also, and somewhat serendipitously, a pyrolytic carbon material developed in the 1960s as a coating for nuclear fuel rods was submitted to the authors' laboratory for possible coating with benzalkonium and heparin. This carbon coating, developed at Gulf General Atomic, Inc, would not bond heparin, but it proved to be the best rigid material available for prosthetic valve construction; more than one million pyrolytic carbon valves have been clinically implanted over the last 29 years (104).

107. The art of descrying distance.

How naive can one experiment be? Imagine asking observers to judge distance -- yes, literally asking them. And in asking them, no visual evoked potentials were measured, and changes in blood flow to the occipital cortex were ignored. But serendipity occurs even to the well-prepared: One's best thought for a new experiment can prove to be one's first unbiased, uncomplicated thought. Here's a cursory review of the events: A number of observers were asked to judge distances between marked posts in a field at night. They made their judgments with the help of night vision goggles (NVG). At first the observers underestimated the distances on average. Then an experimenter began to correct the observers after each judgment. The observers' judgments of distance became accurate. On average, the observers began to estimate those distances accurately (105).

108. Serotonin and drug-induced therapeutic responses in major depression, obsessive-compulsive and panic disorders.

The therapeutic effectiveness of antidepressant drugs in major depression was discovered by pure serendipity. It took over 20 years before the neurobiological modifications that could mediate the antidepressive response were put into evidence. Indeed, whereas the immediate biochemical effects of these drugs had been well documented, their antidepressant action generally does not become apparent before 2 to 3 weeks of treatment. The different classes of antidepressant treatments were subsequently shown to enhance serotonin neurotransmission albeit via different pre- and postsynaptic mechanisms. Clinical trials based on this hypothesis led to the development of treatment strategies producing greater efficacy and more rapid onset of antidepressant action; that, is lithium addition and pindolol combination, respectively. It is expected that the better understanding recently obtained of the mechanism of action of certain antidepressant drugs in obsessive-compulsive and panic disorders will also lead to more effective treatment strategies for those disorders (106).

109. Nobel prize in Medicine and Physiology 1998 for the discovery of the role of nitric oxide as a signalling molecule.

The Nobel Prize for Medicine and Physiology 1998 was awarded to three American pharmacologists: Robert F. Furchgott, Louis J. Ignarro and Ferrid Murad for their work on nitric oxide as a signalling molecule in the cardiovascular system. This discovery is a classical case of serendipity. NO is an endothelium-derived factor which mediates local vasodilation. It protects the vascular system against atherosclerosis by various effects on leukocytes and vascular permeability. NO appears to be a universal signalling molecule in the body, involved in the inflammatory response, apoptosis and neurotransmission. Its biochemistry is closely linked to that of oxygen radicals (107).

110. Antidepressant treatments in the 21st century.

The goal of this review is to provide a provocative discussion of the status of antidepressant treatments in the next century. The first part of the review evaluates the progress (or lack of progress) made in antidepressant medications since the 1950s, when the first chemical antidepressants were discovered by serendipity. The second part then attempts to predict what may be needed to accomplish greater progress in the future, and outlines the types

of approaches that could be used to develop truly novel, and more effective, treatments of depression (108).

111. New visions in the pharmacology of anticonvulsion.

Seizures are resistant to treatment with currently available anticonvulsant drugs in about 1 out of 3 patients with epilepsy. Thus, there is a need for new, more effective anticonvulsant drugs for intractable epilepsy. Furthermore, because of the inadequacy of the currently available anticonvulsant armamentarium with respect to safety, newly developed drugs should be less toxic than existing drugs. Previous and current strategies for development of novel anticonvulsants with improved efficacy or safety are critically discussed in this review. 'Old drugs' (or 'first generation' drugs), which were developed and introduced between 1910 and 1970, are compared with new anticonvulsants both in terms of clinical efficacy and safety and in terms of mechanisms of action. The new drugs are referred to as 'second generation' drugs, i.e. anticonvulsants which have been introduced into clinical practice in recent years, or 'third generation' drugs, i.e. compounds in the pipeline of development. In spite of some 30 years of 'modern' neuroscientific epilepsy research, most novel, clinically effective second generation anticonvulsants have been found by screening (i.e. serendipity) or structural variation of known drugs and not by rational strategies based on knowledge of processes involved in generation of seizures or in development of epilepsy. An exception are only the GABA (gamma-aminobutyrate)-mimetic drugs vigabatrin and tiagabine and, to some extent, gabapentin, which have been developed by a rational strategy, i.e. the 'GABA hypothesis' of epilepsy. The fact that preclinical seizure models used for identification and development of novel drugs have been originally validated by old drugs, i.e. conventional anticonvulsants, may explain that several of the new drugs possess mechanisms which do not differ from those of the standard drugs. This may also explain that none of the new drugs seems to offer any marked advantage towards the old, first generation drugs with respect to the ultimate goal of drug treatment of epilepsy, i.e. complete control of seizures, although some of the second generation drugs may have benefits in terms of side effects and tolerability. It is to be hoped that the various novel currently used or planned strategies for drug development produce more effective and safe anticonvulsants than previous strategies. This goal can only be achieved by strengthening our understanding of the fundamental pathophysiology of seizure expression and epileptogenesis as theoretical substrates for new

pharmacological strategies, and by devising and refining laboratory models for studying new agents obtained by such strategies (109).

112. Early detection of prostate cancer. Serendipity strikes again.

An underappreciated characteristic of prostate cancer screening is that it may detect some prostate cancers solely by serendipity or chance. Serendipity, previously described in the detection of colonic neoplasms, could affect prostate cancer detection when a screening test result is abnormal for reasons other than the presence of prostate cancer, but prostate cancer is coincidentally detected during the subsequent evaluation of the abnormal screening result. We reviewed published articles about prostate cancer screening, searching for evidence of serendipity. We defined serendipity in digital rectal examination (DRE) screening as the discovery of a prostate cancer by the random biopsy of an area of the prostate gland other than the palpable suspicious area that prompted the biopsy. We defined serendipity in prostate-specific antigen (PSA) screening as the discovery of a prostate cancer by the random biopsy of a nonpalpable (stage T1c) prostate cancer less than 1.0 cm³ in volume, since tumors less than 1.0 cm³ are generally too small to cause elevated PSA levels. We found that serendipity may be responsible for the detection of more than one quarter of apparently DRE-detected prostate cancers and up to one quarter of apparently PSA-detected cancers. Additionally, serendipity played a larger role in the detection of smaller tumors that are common but of uncertain clinical significance. We conclude that serendipity-detected prostate cancers contribute to an overestimation of the true information value of DRE and PSA screening. Whether serendipity is advantageous in prostate cancer screening depends on the as yet uncertain outcomes for men with smaller prostate cancers. However, given our estimates of the potential magnitude of the impact of serendipity, the currently popular DRE- and PSA-based screening strategy may not be optimal. If smaller prostate cancers are important, then we are not finding enough; if they are unimportant, then we are finding too many that we may feel compelled to treat aggressively (110).

113. Understanding the unmanageable nursing unit with casemix data. A case study.

The unmanageable nursing unit is one that has the reputation of being wastefully over budget, not using nursing resources well, not cost effective, and certainly not well managed. Serendipity led us to discover ways to understand the unmanageable unit in one institution. The nurse manager

knew the unit was not working well, but had no way to describe this in clinical management terms that would be understood by others. When data from before and after major structural and system redesign initiatives became available, they showed a situation in which decisions were made without data that worked. How much better might it have been had the data that was now accessible been used? We suggest a design for using standard hospital data to define alleged problems of inefficient nursing units, the design is also the structure for monitoring the effects of management changes (111).

114. New light on TRP and TRPL.

Store-operated Ca^{2+} entry, a mode of Ca^{2+} influx activated by depletion of Ca^{2+} from the internal stores, has been detected in a wide variety of cell types and may be the primary mechanism for Ca^{2+} entry in nonexcitable cells. Nevertheless, until recently, no candidate store-operated channel (SOC) had been identified molecularly. Through the serendipity of *Drosophila* genetics, a candidate SOC, referred to as Transient Receptor Potential (TRP), has been identified that is essential for the light-induced cation conductance in photoreceptor cells. A combination of in vitro and in vivo studies has provided strong evidence that TRP is a bona fide SOC. Moreover, TRP forms a supramolecular complex, proposed to be critical for feedback regulation and/or activation, that includes rhodopsin, phospholipase C, protein kinase C, calmodulin, and the PDZ domain-containing protein, INAD. INAD seems to be a scaffolding protein that links TRP with several of these other proteins in the complex. TRP also complexes with a related channel subunit, TRP-like, to form a heteromultimer with conductance characteristics distinct from those of TRP or TRP-like homomultimers. A family of proteins related to TRP is conserved from *Caenorhabditis elegans* to humans, and recent evidence indicates that at least some of these proteins are SOCs. The human TRP-related proteins may mediate many of the store-operated conductances that have been identified previously in a plethora of human cells (112).

115. Significance of cognitive processes in drug research in the 19th century--exemplified by nitroglycerin.

The history of the discovery and development of drugs is replete with examples where chance and "serendipity" have resulted in important advances of knowledge. In the case of nitroglycerin it can be shown that what appears to have been a chance discovery was actually the result of a sequence of selective perceptions by, and cognitive processes in individual researchers. The sources allow insight into various stages of the development

of nitroglycerin, starting with the chemical synthesis as an explosive in 1846 and the first use in humans in 1847 to the discovery of a useful coronary drug. Homeopathic medicine contributed significantly to this process. Thus, the history of nitroglycerin is an example of an exchange of knowledge between otherwise separate realms of sectarian and orthodox medicine in the second half of the 19th century (113).

116. Illumination of therapeutics by toxicology: a personal view.

"1. My specialties are therapeutics and toxicology. When we think in classical terms about drugs, therapeutics refers to curative healing, toxicology to the capacity to produce harm. However, they are not opposite disciplines, but rather reflect a continuum along the dose-response curve of a drug or toxin. Since antiquity, the study of toxicology has underpinned and illuminated therapeutics. Even the most potent toxins, such as botulinum and ricin, are used for therapeutic purposes. 2. In the case of one of my favourite research topics, the herbicide paraquat, I illustrate how investigating methods to treat patients poisoned by it has led to important advances in knowledge in medicine and therapeutics. Studying paraquat has launched my own research group on a path towards elucidating the mechanisms of the chronic neurological side effects of the antipsychotic drug, haloperidol, which is used widely to treat schizophrenia. In tracing these tortuous paths, the roles that serendipity and creativity play in research and their implications for education and funding policies are high-lighted" (114).

117. Finding health resources on the Internet--the departure lounge.

As with all other areas of research, the influence of the Internet on health economics will continue to grow. The availability of information is central to the UK health reforms and plans are afoot to create an NHS network. Harnessing the power of the Net has become a basic research skill. This involves information and data capture, work sharing and communication as well as dissemination of our own work findings. You might optimistically regard the Internet as a system of arteries and arterioles through which oxygen of information may flow effectively to those who need it. However, users are sometimes frustrated by slow access, poorly indexed information and lots of noise: successful use sometimes seems reliant on serendipity. The Departure Lounge will try to keep you up to speed with developments (115).

118. Intracavernous pharmacotherapy: treatment for the aging erectile response.

Fueled by serendipity, observation, and direct scientific investigations over the last 15 years the normal mechanisms of erection, and the pathophysiology of erectile dysfunction have been revealed. The demonstrations that vasoactive injections could produce penile erection without benefit of psychic or tactile stimuli revolutionized the diagnosis and treatment of erectile dysfunction by providing a direct test of end organ integrity or deficiency (116).

119. Glen W. Hartman Lecture. Science, creativity, and serendipity.

In this Roentgen centennial year, honoring the epochal discovery of the X-ray in 1895, it is particularly appropriate to reflect on the circumstances of creativity that lead to important discoveries in science. In radiology as in general medicine and surgery, histories of the development of the discipline have generally presented a chronicle of sequential events without specific consideration of the underlying creative impulse. I wish to consider features of creativity that may be relevant to us, that may enlighten us, and that may allow us to incorporate them individually into our view of the world and our appreciation of the grandeur of such contributions (117).

120. Gastric emptying is impaired in patients with spinal cord injury.

The rate and completeness of gastric emptying (GE) are major determinants of the bioavailability of oral medication, and the efficiency of gastric emptying is highly dependent on an intact central nervous system. Hence, in spinal cord injury (SCI), an impairment in gastric emptying could significantly diminish drug efficacy.

We evaluated posture-dependent (seated and supine) gastric emptying of an isotopically-labeled liquid meal in six quadriplegic subjects. The time-course profile of the gastric elimination of a radionuclide was followed for up to 120 min using serial anterior scintigraphy, and the disappearance of radioactivity from the stomach was described by both a mono- and biexponential fit of raw data. A half-time of gastric emptying (GEt_{1/2}) was estimated from each curve and compared to GEt_{1/2} derived from able-bodied (intact neuraxis) experimental and historic control populations.

The mean GEt_{1/2} in quadriplegic subjects (monoexponential curve fit) was significantly increased to 43.4 +/- 26.0 min in seated SCI subjects (95% CI 13.5-73.2, p < 0.05) and to 50.5 +/- 48.0 min in supine SCI subjects compared to supine experimental and historic control values of 10.1 +/- 8.8 min (95% CI 2.3-18.0, p < 0.05) or 12.0 +/- 3.0 min (95% CI 9.4-14.8, p < 0.05),

respectively. A small, non-significant trend towards an increased rate of GE (decreased GEt1/2) was observed in seated SCI subjects.

We conclude that gastric emptying is impaired in subjects with cervical SCI. Comparative studies of gastric emptying in subjects with SCI should incorporate concurrently studied, control subjects and employ experimental methods that are not constrained by truncated data collection periods. The convention of forcing GE data to conform to a monoexponential pattern of evacuation ignores time-dependent multiphasic patterns of GE and does not support serendipity (118).

121. Genetic models of human vascular disease.

The use of genetic models has greatly assisted investigations of the natural history, mechanisms, and potential therapy for human vascular disease. In the past, genetic models of vascular disease were obtained through serendipity and/or selective breeding to obtain inbred lines that express the phenotype of interest. This approach has yielded several valuable models of atherosclerosis and hypertension. In the past several years, the advent of molecular techniques has enabled investigators to produce additional novel genetic models of disease that have further enhanced the study of vascular biology and medicine. Transgenic techniques and the techniques of homologous recombination have allowed researchers to alter the genotype of an animal in a precise manner and to study the resultant change in phenotype. More recently, techniques of in vivo gene transfer have also accelerated and enhanced the development of novel models. The application of these methodologies has resulted in important breakthroughs in our understanding of the pathogenesis and treatment of vascular diseases (119).

122. The history of interventional cardiology: cardiac catheterization, angioplasty, and related interventions.

The histories of cardiac catheterization, angioplasty, and other catheter interventions are spectacular journeys marked by undeterred genius, serendipity, and the vindication of the scientific method. Cardiac catheterization began with Hales's 1711 equine biventricular catheterization, other early experimental catheterizations in the nineteenth century, and Forssmann's dramatic 1929 right-heart self-catheterization. Courmand, Richards, and others finished unlocking the right heart in the 1940s; Zimmerman, Cope, Ross, and others unlocked the left heart in the 1950s; and

the coronary arteries were inadvertently unlocked by Sones in 1958, leading to the advent of percutaneous femoral coronary angiography by Judkins and by Amplatz in 1967. Dotter's accidental catheter recanalization of a peripheral artery in 1963 ushered in the era of intervention, crowned by Gruentzig's balloon angioplasty in the mid-1970s and leading to today's panoply of devices used percutaneously to revascularize the coronary arteries in a variety of clinical settings (120).

123. Reorganization of the information technology program at a United States medical school: is there a lesson for academic medical informatics in Japan?

Reorganization of the information technology program at Baylor College of Medicine commenced with the goal of obtaining a client-focused organization instead of a classically departmental structure. Legacy organizations independently established by request or serendipity had gaps and overlaps in services and could no longer respond to new issues, such as integration of several hospitals, resource sharing of health care delivery, administration of a shared library, and an academic informatics program. The renewal of the information technology program has led to departments of Telecommunications, Enterprise Services, Client Services, and Medical Informatics, and has also allowed cross-departmental projects led by a technology architect. In contrast with that of Baylor, the approach of the Yamaguchi University School of Medicine in Japan may be construed as economic efficiency at the cost of client services. Effective client services by friendly and efficient staff groups is the most important factor for an academic information technology program, if the goal is to reorganize in anticipation of future challenges to the medical center (121).

124. Antidepressant drug selection: criteria and options.

The dilemma of developing new medications rationally--as opposed to discovering them through serendipity--is to create an optimal balance between the number of mechanisms of action needed for the widest spectrum of antidepressant activity while maximizing safety and tolerability. Newer antidepressants, such as serotonin selective reuptake inhibitors (SSRIs) and venlafaxine, have a wider therapeutic index than the older tricyclic antidepressants. Fewer types of adverse effects and a reduction in the potential for pharmacodynamic interactions are the distinct benefits of all the newer targeted antidepressants, such as venlafaxine, SSRIs, and bupropion, in comparison with older drugs. However, there are important differences

among the newer antidepressants in terms of effects of P450 enzymes, dose-response curves for antidepressant response and adverse effects, and dosing schedules. One of the main benefits of having a wide array of options is the evidence that there may be different forms of the illness, which respond to different mechanisms of action. More research is needed to test this concept and to develop predictors of differential responsiveness (122).

125. Primary empty sella syndrome. Report of 6 cases.

The extension of the suprasellar subarachnoid space through an incompetent diaphragma sellae into the sella turcica is defined as empty sella syndrome (ESS). The primary form arises in the absence of previous pituitary surgery or irradiation. Predominance of obese, middle aged, often multiparous women are generally observed; clinically headaches and slight endocrine alterations are frequent but not characteristic symptoms. Rarely liquor rhinorrhea or visual campimetric defects may occur. The authors report six cases observed in their Departments of Internal Medicine during the last two years; they discuss the aspecific symptoms of presentation and the associated pathologic conditions. Standard skull X rays were negative in half the cases showing the overall poor sensitivity of this examination in detecting ESS. According to the literature no evident abnormality of hypophyseal basal hormone levels was found. Diagnosis was done by high resolution TC or MR which now must be preferred to pneumoencephalography (PEG). Three patients had peculiar pathologic conditions associated with ESS: a very high suspicion of partial insipidus diabetes was made in a man with hypo-osmolar polyuria; one patient without related humoral symptoms had a duodenal carcinoid endoscopically removed and in another primary ESS was associated with Hashimoto thyroiditis. These last two pathologies were never related before associated to primary ESS. The authors conclude that primary ESS is most often a diagnosis made by serendipity, lacking specific signs and or symptoms, whenever an imaging technique (TC or MR) is employed for detecting an unrelated endocrinic pathology or the content of an enlarged sella turcica (123).

126. Community and university--partners in research.

Community-based and university-based family practice researchers must come together and merge into a synergistic partnership. Community-based researchers often need the special expertise of university statisticians, epidemiologists, and research methodologists, and the enthusiasm of fellow

researchers. University-based researchers look to the community for subjects and the all-important factor of generalizability. We must no longer rely on serendipity to bring community- and university-based researchers together. Community-based people must acknowledge their needs and actively seek out assistance. The university-based departments can respond by deliberately starting outreach programs, setting up buddy systems, engaging community research consultants, and tracking residents and urging them to continue to do research. Sentinel networks can increase the depth of involvement community researchers have with their own, and others' projects. Such efforts will lead to a creative interrelationship that will be rewarding and enjoyable for us all (124).

127. The Klippel-Feil syndrome: implications for Naval service.

The Klippel-Feil anomaly is usually discovered by serendipity on cervical spine X-rays. Although it may encompass many vertebrae, the typical case is an isolated fusion of two vertebrae. Nearly 1% of the general population has this anomaly and its incidence in the Navy is likely similar. Increased susceptibility to spinal cord injury has been reported in individuals with the Klippel-Feil syndrome. Unusual stress on the head and neck inherent to various aspects of naval service place such persons at risk for debilitating or fatal injury (125).

128. Molecular biology of the 2-oxo-acid dehydrogenase complexes and anti-mitochondrial antibodies.

The confluence of molecular biology and clinical medicine has provided new and valuable insights in PBC. Our understanding of the immunobiology of PBC has changed dramatically using this new technology. It is now possible to explicitly define mitochondrial autoantigens and examine recognition sites, by using autoantibodies, at the primary sequence level. In addition, cloned antigens have been developed to reliably assay for presence of autoantibodies; the use of cloned recombinant antigens should replace that of traditional immunofluorescence for AMA assay. It is also now possible to begin the task of defining the role of T cells in the immunopathology of PBC and exploring the issue of whether immunotherapy is possible. Finally, there is increasing evidence that PDC-E2 is located on the cell membrane of biliary epithelial cells. The mechanism for this expression remains to be studied. The explosion of data in PBC is an example of the serendipity and synergy brought about by application of new techniques to investigate old problems (126).

129. Oncologic imaging. Staging and follow-up of renal and adrenal carcinoma.

Computed tomography (CT) has emerged from the 1980s to play a dominant role in the pretreatment staging of renal and adrenal carcinomas. For detection, definition (staging), and determination of resectability or recurrence, CT with intravenous contrast enhancement, and more recently, magnetic resonance imaging (MRI) with gadolinium-DTPA, may be the only cross-sectional imaging studies required before institution of appropriate therapy. Carcinoma of the kidney is frequently diagnosed by serendipity or detected on incidental ultrasound or CT examinations. Real-time ultrasound and color flow Doppler offer unique information on tumor vascularity and major venous vascular involvement. Positive predictive values of 96% can be achieved for the diagnosis of renal cell carcinoma using contrast-enhanced CT scanning. For follow-up CT and MRI are the best imaging techniques for evaluation of the retroperitoneum. MRI may distinguish tumor recurrence from fibrosis in selected cases. Because primary neoplasms of the adrenal gland are rare and often exceed 10 cm at the time of initial diagnosis, the functional nature (endocrine) of adrenal carcinoma may be part of the clinical presentation. Because initial stage is critical to survival and extent of surgical therapy, a knowledge of tumor classification is essential to the optimal diagnostic evaluation. Newer imaging tests, CT and MRI, have superseded conventional urography, ultrasound, and radionuclide studies for the diagnosis and staging of adrenal cancer. Early diagnosis and low stage at presentation are critical to survival in patients with adrenal carcinoma. The current concepts for pretreatment imaging evaluation and the role of CT, MRI, and ultrasound are outlined. An oncologic imaging approach based on tumor staging and classification for patients with real or suspected renal cell carcinoma and adrenal carcinoma is essential to optimal patient care (127).

130. Serendipity--its basis and importance.

Horace Walpole (1717-1797) coined the term serendipity in 1754 in allusion to an ancient oriental legend of the "Three Princes of Serendip". Since about one century this term has been discussed in literary history; for almost 50 years medical writers have made use of it. Today, serendipity is understood as the ability to make discoveries not purposely searched for - the greater the knowledge, the more likely the discovery (128).

131. Osteopathic medicine and primary care practice: plan or serendipity?

General practitioners predominate in osteopathic medicine (57% of all D.O.s), as compared with allopathic medicine. A number of possible reasons are put forth: the student selection process (cloning by admission committee general practitioners); special features of osteopathic education (more required courses, primary care courses, and rotations); training in osteopathic hospitals (mainly community institutions); a required rotating internship; and predominant departments of general practice in osteopathic hospitals and colleges (providing more high-quality general practitioner role models). The author suggests consideration of personality differences, as measured by the Myers-Briggs Type Indicator, as a possible causative factor in differences between the allopathic and osteopathic segments of medicine (129).

132. Small adenomas detected during fecal occult blood test screening for colorectal cancer. The impact of serendipity.

Yearly fecal occult blood testing (FOBT) has been recommended for men and women over age 50 years as part of a screening regimen intended to reduce colorectal cancer mortality. The primary targets of screening are early, surgically curable colon cancers and large adenomatous colon polyps; however, screening may sometimes reveal only small adenomas (ie, less than 1 cm in diameter). To assess the rates and mechanisms of FOBT detection of small adenomas, we performed quantitative analyses utilizing estimates of adenoma bleeding rates and FOBT sensitivity and specificity. The analysis suggests that the mechanisms of detection of small adenomas is often chance or serendipity. This occurs when an FOBT result is "falsely" positive because of diet or non-neoplastic gastrointestinal bleeding and leads to colonoscopic discovery of a nonbleeding small adenoma. Nevertheless, small adenomas remain undetected in most persons who have them, even if repeated yearly FOBT screening is done. The identification of persons with small adenomas should not be assumed to be an important beneficial outcome of FOBT screening, because the clinical significance of small adenomas is not clear, the mechanism of detection is serendipity, and only a minority of persons with small adenomas are identified. The current recommendations to perform periodic surveillance colonoscopy following removal of small adenomas detected during FOBT screening should be reexamined (130).

133. Parasitological serendipity: from *Schistocephalus* to *Echinococcus*.

Attention is drawn to the situation nowadays, whereby workers are encouraged to undertake research which appears useful or of economic

importance, although the History of Science indicates that many major discoveries have been the result of 'serendipity'--'the chance observation falling on the receptive eye'. Some of the more important examples in Medicine and Parasitology are reviewed. The author then relates how he was given a stickleback infected with the plerocercoid of *Schistocephalus solidus*, an episode which eventually led to the successful in vitro culture of the adult of this species. Attention is also drawn to the largely unrecognized work of the Danish Veterinarian, P. C. Abildgaard, who in 1789 demonstrated that this species completed its life cycle in a bird, thus establishing, for the first time, the transmission of a parasite from one host to another. The in vitro culture of *S. solidus* led to the development of successful in vitro techniques for *Ligula intestinalis* and for *Echinococcus granulosus* and *E. multilocularis*. The observation that *E. granulosus* of horse origin failed to grow in vitro led eventually to the concept of physiological 'strains' of *E. granulosus*, now a subject of much international research (131).

134. Towards a rationalization of biological psychiatry: a study in psychobiological epistemology.

Contemporary biological psychiatry is in a seemingly inchoate state. I assert that this state of biological psychiatry is due to its violation of an epistemological criterion of rationality, i.e., the relevance criterion; that is, contemporary biological psychiatry is irrational as it adopts a conception irrelevant to the psychobiological domain. This conception is mechanistic. The irrationality of biological psychiatry is manifest as the dominance of neurochemical explanations of psychopharmacological correlations, resulting in predictive sterility and, correspondingly, in the dominance of serendipity. I suggest a rationalization of biological psychiatry through a conception relevant to the psychobiological domain. This conception is hierarchical (132).

135. Studies on inborn errors of metabolism in Norway.

Some 50 years ago, Müller described hypercholesterolemia, xanthomas, and coronary heart disease as symptoms of a genetic disorder. In the 1930s, other important discoveries concerning inborn errors of metabolism were made in Norway. Følling described phenylketonuria, and Refsum examined his first patients with hereditary ataxia polyneuriticiformis (phytanic acid storage disease). Several other inborn errors of metabolism have been discovered in Norway: familial lecithin-cholesterol acyltransferase deficiency, methylmalonic acidemia, beta-methylcrotonyl-coenzyme A carboxylase deficiency, pyroglutamic aciduria, and N-acetyl aspartic aciduria. Metabolic and

biochemical studies in these patients have revealed new and important metabolic pathways. Studies on patients with inborn errors not first described in Norway have also given important information on key enzymes in metabolic pathways. Thus, studies on patients with cerebrotendinous xanthomatosis and those with Zellweger's syndrome have revealed the normal metabolic route for conversion of cholesterol to bile acids. The discoveries and the clinical and biochemical research in former days were mostly good examples of serendipity combined with excellent clinical alertness. In more recent years, several of the discoveries have resulted from systematic biochemical screening of urine, plasma, or other body fluids from patients with unusual clinical syndromes (133).

136. Diagnosis of patent ductus arteriosus by serendipity in the adult.

Seven patients with patent ductus arteriosus (PDA) were seen in our adult echocardiography laboratory. In five of seven patients the diagnosis was made on color Doppler when it was not suspected clinically. The diagnosis became apparent because of a turbulent retrograde jet seen on color Doppler in the main pulmonary artery. One of the patients had known congenital heart disease and heart surgery in the past, and the diagnosis of PDA was missed both on catheterization and in the operating room. PDA may be unsuspected in adult patients and may be missed by techniques other than color Doppler echocardiography. The striking findings on color Doppler may help to make this important diagnosis in such patients (134).

137. Discursive thought and intuition in medical research.

The history of diabetes and the progress of the sciences demonstrates that original creative investigation requires in addition to logic thinking intuition which originates from the unconscious. The concept of intuition is of great importance in philosophy, religion and psychology. Luck and serendipity have similar meaning as the concepts of *kairos*, *tyche* and *techne* of the Greek (135).

138. Serendipity in biological psychiatry--a myth?

It is often stated that major biological treatments in psychiatry were discovered by accident or serendipity. Tracing the history of the concept of serendipity, we find that serendipity has been subjected to greatly divergent interpretations. According to the current usage, it is a discovery in which chance was a necessary and/or sufficient condition. With this definition, none of the discoveries of major biological treatments in psychiatry can be labeled

serendipitous. The necessary factors common to these discoveries were creative minds that were variably influenced by the zeitgeist and that were persistent in their search for answers. Another important prerequisite was the availability of crucial basic knowledge of many related sciences. We conclude that chance cannot substitute for long-term research and that the latter is the most likely way to lead to valuable discoveries (136).

139. Toward standardized usage of the word serendipity in the historiography of psychopharmacology.

Contradictory views are expressed in the literature about the role played by serendipity in discoveries that led to modern psychopharmacology. This article attempts to resolve these contradictions by providing an operational definition of serendipity. The utility of the proposed definition is explored in the context of 18 discoveries. The results show that the most common pattern in the development of early psychiatric medications is serendipitous observation leading to non-serendipitous demonstration of clinical utility. The analysis also reveals examples of relatively pure serendipitous and non-serendipitous discoveries. The proposed definition appears to be reliable and valid (137).

140. History of early ultrasonic blood flowmeters.

Methods of measuring flow of fluids by acoustic techniques before 1960 are reported, and motivation for such documentation is presented. Serendipity played a role in introducing acoustic flowmeters to the Institute of Experimental Medicine of the Mayo Graduate School of Medicine. Ultrasonic flowmeters promise to be clinically useful in procuring dimensions of blood vessels, in measuring flow transcutaneously, and in studying the dynamics of flowing blood within the diseased cardiovascular system (138).

141. Renal serendipity in whole body scintiscan.

The importance in nuclear medicine procedures of critical examination of all of the data, beyond the problem in question, is emphasized. These case reports exemplify such situations. Renal pathology was diagnosed serendipitously while performing skeletal screening in patients in whom renal diseases had not been thought of (139).

140. A history of sweeteners--natural and synthetic.

Sweetness for the prehistoric man was the taste sensation obtained from sweet berries and honey. Man's quest for other sweet things led to sucrose, starch-derived sugars, and synthetic sweeteners. An unusual source of sweet

taste is a West African berry known as miracle fruit (*Synsepalum dulcificum*). This fruit possesses a taste-modifying substance that causes sour foods--e.g., lemons, limes, or grapefruit--to taste sweet. The active principle was found to be a glycoprotein. Until this time, only small molecules were considered sweet-evoking substances, but now macromolecules are considered capable of participating in taste perception. The intense sweetener of the fruit of *Dioscoreophyllum cumminsii*, called the serendipity berry, was revealed to be a protein. The intensely sweet principle of *Thaumatococcus daniellii*, called katemfe, was reported in 1972 to contain two proteins having intense sweetness. Since intensely sweet protein sweeteners act directly on taste buds as a probe, a peptide linkage analogous to the aspartic acid sweeteners may be partly responsible for their sweetness (140).

143. Happy Accidents: Serendipity in Modern Medical Breakthroughs

"Dr. Meyers, who has been one of leading abdominal radiologists in the world for more than 30 years, has recently written a book entitled "Happy Accidents: Serendipity in Modern Medical Breakthroughs." While I am reading the book, I feel an urge to introduce this book to all readers of the *Korean Journal of Radiology*. This book is based on a long experience and feeling on the modern medical breakthroughs of one talented and experienced abdominal radiologist.

In his book, Dr. Meyers is saying that medical discoveries in history came about because someone stumbled upon an answer and after some creative thought, figured out what problem had to be inadvertently solved. In science, surprising observations that lead to the development of several great commercial products happen all the time, but they have generally been kept secret. Opportunities for discovery present themselves every day, but not every one is able to take advantage of them.

Dr. Meyers asserts that fostering serendipity is important. He is saying that money does not foster new ideas, at least ideas that drive science; it only fosters applications of old ideas, most often enabling improvements but not discoveries. Only ideas and creative thought can provide an answer, and the ideas and creative thought are things that our existing system sadly lacks and fails to nurture. Serendipitous discoverers insist on trying to see beyond their own and others' expectations and resist any pressure that would close off investigation. They break through, sidestep, or ignore any obstacle or objection to their chosen course.

Dr. Meyers has some concern over the peer review system that is currently employed for the NIH grant application or journal review system. He is insisting that in the current review system, research has come to be characterized by large teams drawing upon multiple scientific disciplines and using highly technical methods in an environment that promotes the not-very-creative phenomenon known as groupthink. Researchers and Big Pharma generally disregard "niche" diseases, those affecting so few people that a

breakthrough treatment would not lead to glory or profit. Peer review institutionalizes dogmatism by promoting orthodoxy. Who on a review committee is the peer of a maverick?

Finally, Dr. Meyers concludes that discoveries are surprises. You cannot plan surprise, but you can certainly create an environment in which they are apt to happen and are likely to be recognized and pursued when they do. Fostering openness to serendipity has the potential to accelerate medical discovery as never before.

I would like to recommend reading this book to my two sons who are students in engineering and medicine, respectively, to interns, residents and young medical investigators in my hospital, and finally to the readers of the *Korean Journal of Radiology*. Furthermore, I can say that to foster serendipity, 'please be alert to new ideas and happenings and keep your imagination roaming' as Dr. Meyers has insisted" (141).

144. AB005. The role of serendipity in sexual medicine

The word "serendipity" is considered very difficult to define; it may be considered "A talent for making fortunate discoveries while searching for other things". The history of sexual medicine teaches us the importance of serendipity along with research. Serendipity in the year 1988 was initiated by a slow elevator. Dr. Jacob Rajfer, Professor of Urology, had attended a meeting on the 2nd floor of the Univ. California LA and was waiting for an elevator to take him to his office on the 6th floor. The elevator was very slow to arrive, so Dr. Rajfer began looking around. There was a sign on a door across from the elevator that read: "Vascular smooth muscle lab". Dr. Rajfer knew that an unknown substance, Endothelium-derived Relaxing Factor (EDRF) dilated blood vessels by relaxing smooth muscles. A penile erection resulted from vasodilation and the penis was full of vascular smooth muscle. The head of the vascular smooth muscle lab was Dr. Louis Ignarro who had just published that EDRF might be Nitric Oxide (NO). Drs. Rajfer and Ignarro began collaborating, and in 1990 published that 'NO' mediates erections: a discovery started by a slow elevator and leading to Dr. Ignarro receiving a Nobel Prize in 1998 and Pfizer scientists developing Viagra! Viagra, which was able to dilate smooth muscle, was being developed by Pfizer researchers to treat angina when increased nocturnal and spontaneous erections were noted. The FDA approved Viagra as the first oral treatment for erectile dysfunction in 1998. Serendipity, research and Viagra impacted how we look at aging and intimacy. The language of sexual medicine changed as well: the old term, 'impotence' (lacking in power) was changed to 'erectile dysfunction' or ED. Serendipity has played a role in the discovery of more than 24% of all drugs on the market. We would all do well to heed the wise words of Louis Pasteur: "Chance Favors the Prepared Mind" (142).

145. Serendipity in medicine and anesthesiology.

This study has evaluated more than a hundred of the most fortunate couplings of a brilliant mind with fortunate luck (serendipity), through the re-reading of

most relevant histories on science-related (n = 46) and anesthesiology-related (n = 16) inventions and discoveries.

This educational article encourages anesthesiologists to appreciate events related to scientific inventions and discoveries, showing that serendipity is possible, provided it is expected. Each discovery or invention includes history, references and scientific or anecdotal explanation. In addition to traditional discoveries, such as wine, gravity, photograph, Velcro, airbag, etc., there are other Medicine-related (microscope, X-rays, vaccine, penicillin, insulin, laser, Paps smear, etc.) and Anesthesiology-related (isometry, gloves, N₂O, ether, barbiturates, benzodiazepines, blood patch, etc.) discoveries. Creativity and serendipity may act as cornerstones for clinical and basic research of pioneer inventions for medical and anesthesiologic advances. In fact, topics related to biology, anatomy, physics, chemistry, physiology, pharmacology, astronomy and archeology should be master and lots of luck.

Although research and operating room accidents are regrettable, some of them happen and may sometimes lead to spectacular advances, such as heroic treatments and even Nobel Prizes. Open-mindedness is a common trait to those willing to count on grand prize, as American physicist Henry would state (1842): 'Seeds of discovery are constantly floating around us, but the only take roots in minds well prepared to receive them' (143).

146. Eureka! When Scientists Find What They're Not Looking For

(144)"In my new book *Happy Accidents: Serendipity in Modern Medical Breakthroughs*, (145) I reveal a great secret of modern medicine: Many of the pivotal discoveries of the past century, which have saved or enhanced innumerable lives, came about as a result of happenstance. Scientists with open, creative minds stumbled across surprising results, and found what they were not looking for.

Chemotherapy drugs, (146) the psychotropics, (147) many antibiotics, (148) the bacterial cause of stomach ulcers, (149) the source of adult stem cells (150) and the genetics of cancer (151) – all were discovered by chance.

Only years later is the truth disclosed in memoirs, prize acceptance speeches, and in interviews I conducted with a number of Nobel laureates and recipients of other prestigious awards.

One approach to medical discovery is the centralized management of directed research. The experience of more than 3 decades with a War on Cancer directed and funded by the federal government has shown the futility of this approach. The better approach is based on independent, creative, curiosity-driven research that liberates serendipity. It is this approach that has brought

us the bountiful results mentioned previously. We need to be sound in our judgment of the allocation of funding and resources.

Fostering an openness to serendipity has the potential to accelerate medical discovery as never before. Here are my specific prescriptions:

First: Students, particularly in science and medicine, must be taught about the role of serendipity and be prepared to recognize and exploit departures from expected results. Indeed, chance does favor the prepared mind.

Second: Restrictions should be placed on Big Pharma to shift the emphasis from 'me-too' drugs to innovative drugs(152).

Third: Agencies and foundations that fund research grants should allow curiosity-driven investigators to pursue any unexpected findings wherever they may lead.

Fourth: The process of peer review should be modified to reduce the inherent bias toward prevailing concepts and to welcome mavericks and outsiders.

That's my opinion; I'm Dr. Morton Meyers, Emeritus Professor of Radiology and Medicine, SUNY, Stony Brook."

147. The Beneficial Role of Mobility for the Emergence of Innovation.

Innovation is a key ingredient for the evolution of several systems, including social and biological ones. Focused investigations and lateral thinking may lead to innovation, as well as serendipity and other random discovery processes. Some individuals are talented at proposing innovation (say innovators), while others at deeply exploring proposed novelties, at getting further insights on a theory, or at developing products, services, and so on (say developers). This separation in terms of innovators and developers raises an issue of paramount importance: under which conditions a system is able to maintain innovators? According to a simple model, this work investigates the evolutionary dynamics that characterize the emergence of innovation. In particular, we consider a population of innovators and developers, in which agents form small groups whose composition is crucial for their payoff. The latter depends on the heterogeneity of the formed groups, on the amount of innovators they include, and on an award-factor that represents the policy of the system for promoting innovation. Under the hypothesis that a "mobility" effect may support the emergence of innovation, we compare the equilibria reached by our population in different cases. Results confirm the beneficial role of "mobility", and the emergence of further interesting phenomena (153).

148. Designing multi-targeted agents: An emerging anticancer drug discovery paradigm.

The dominant paradigm in drug discovery is to design ligands with maximum selectivity to act on individual drug targets. With the target-based approach, many new chemical entities have been discovered, developed, and further approved as drugs. However, there are a large number of complex diseases such as cancer that cannot be effectively treated or cured only with one medicine to modulate the biological function of a single target. As simultaneous intervention of two (or multiple) cancer progression relevant targets has shown improved therapeutic efficacy, the innovation of multi-targeted drugs has become a promising and prevailing research topic and numerous multi-targeted anticancer agents are currently at various developmental stages. However, most multi-pharmacophore scaffolds are usually discovered by serendipity or screening, while rational design by combining existing pharmacophore scaffolds remains an enormous challenge (154).

149. Bioactivity-guided mixed synthesis accelerate the serendipity in lead optimization: Discovery of fungicidal homodrimanyl amides.

The bioactivity-guided mixed synthesis was conceived, in which the designed mix-reactions were run in parallel for simultaneous construction of different kinds of analogs. The valuable ones were protruded by biological screening. This tactic will facilitate more rapid incorporation of bioactive candidates into pesticide chemists' repertoire, exemplified by the optimization of less explored homodrimanes as antifungal ingredients. The discovery of D9 as a potent fungicidal agent can be completed in <2 weeks by one student, with EC_{50} of 3.33 mg/L and 2.45 mg/L against *S. sclerotiorum* and *B. cinerea*, respectively. To confirm the practicability, time-efficiency, and reliability, specific homodrimanes (82 derivatives) were synthesized and elucidated separately and determined for EC_{50} values. The SAR correlated well with the intentionally mixed synthesis and the potential was further confirmed by the *in vivo* bioassay. This methodology will foster more efficient exploration of biologically relevant chemical space of natural products in pesticide discovery, and can also be tailored readily for the lead optimization in medicinal chemistry (155).

150. Isoprene research - 60 years later, the biology is still enigmatic.

Isoprene emission is a major component of biosphere-atmosphere interactions. It is the single largest source of non-methane hydrocarbon in the atmosphere. The first report of isoprene emission from plants was published in 1957 by Professor Guivi Sanadze. While humans have smelled the monoterpene hydrocarbons made by coniferous trees since their earliest migrations, only in 1957 did the world become aware that other trees make a type of hydrocarbon in even greater amounts but one to which the human nose is much less sensitive. For this 60th anniversary of the first report of isoprene emission from leaves, we trace the discovery and development of the research field, highlighting some of the most seminal observations and theoretical interpretations (156).

151. Looking Back while Stepping Forward-A Path Made Possible by Serendipity, a Few Good Decisions, and Helpful Colleagues.

" I am in a sweet spot in life, and I have been reflecting on what is special about my circumstances and how they came to be. This introspection has focused my attention on determining why my dermatology research career has been rewarding, identifying people and occurrences that have been influential and recommitting to helping others become similarly fortunate. Fifty years ago, I could not have predicted my career path, or imagine the life experiences that I have had and that I value highly. Perhaps "my story" will be interesting and/or encouraging to some.

I grew up in a small town in the Midwest (population approximately 9,000), the son of a tool and die maker and a schoolteacher. My friends were all Caucasian protestants, their fathers' collars were blue, and their mothers were homemakers. Our houses and our expectations were modest, and life was pretty simple. My world view was small, expanded even by Saturday nights' "The Jackie Gleason Show" and, later, "The Honeymooners" featuring vignettes depicting Ralph Kramden's fictitious life as a bus driver in New York City. Lucky for me, public education was a high priority in Wisconsin in the 1960s and the 1970s, and I had excellent teachers in elementary, middle, and high school.

Thus, I was surprisingly well prepared to become a Chemistry major at the University of Wisconsin, where there were more people living in my freshman dormitory complex than in my entire hometown. Somehow I talked a prominent organic photochemist, the late Howard Zimmerman, into letting me

begin to do “independent research” with one of his postdoctoral fellows after my freshman year. If this had not happened, I think that I would never have had a bench research career, because I was not excited by the “cookbook” laboratory experiences that were associated with my undergraduate science courses.

I had no exposure to medicine before, or during, my undergraduate years, but I completed the typical “pre-med” courses out of interest. I became friends with Michael Green, now Director of the UMass Cancer Center, as a freshman and both of us benefitted from his father’s advice. Maurice Green, a prominent St. Louis virologist, recommended obtaining an MD, rather than a PhD, degree because, at the time, physicians had easier access to funding than nonphysicians, and physicians also earned higher salaries. Michael subsequently introduced me to Washington University, an institution that I had never heard of. He and I both entered the MD, PhD program at Washington University in 1975. Electing to become a physician is the best professional decision that I have made.

I met the late Charles Parker, an allergist, immunologist, and closet organic chemist, during my first summer in St. Louis and later did my PhD thesis work in his laboratory, where I was surrounded by young physician scientists. We investigated human lymphocyte activation at a time when T-cell subpopulations were just being identified, the structures of T-cell antigen receptors and major histocompatibility complex antigens were unknown, and the primary in vitro readout for lymphocyte activation was proliferation. In retrospect, we were terribly naïve about the immune system and our entirely too preliminary studies resulted in publications, but few meaningful insights. However, during one late night conversation in the laboratory, Charlie Fischman (a clinical allergy fellow) informed me that he had identified a career path for me. Charlie opined that if I became a dermatologist, I could learn about and care for patients with interesting inflammatory diseases and still have time to do laboratory research. This sounded pretty good to me, and senior colleagues put me in touch with the dermatologists at Washington University to learn more.

The Dermatology Division at Washington University has a long tradition of dermatologic research excellence. In the 1970s and 1980s, it was a powerhouse, emphasizing studies of collagen metabolism (especially collagen degradation). Arthur Eisen was the Chief of the Division, and Eugene Bauer,

Jouni Uitto, Howard Welgus, George Stricklin, John Jeffrey, Jo Selzter, Greg Goldberg, and Lynn Cornelius were all affiliated as faculty members or trainees. These individuals encouraged me to become a dermatologist and, after a year as a Medicine intern at Barnes Hospital, I became a dermatology resident—dividing my time between the clinics and a cellular immunology laboratory in Pathology. This 3-year period was a time of intense learning. I sought to study suppressor T cells in an autoimmune disease model, but my productivity was limited. Despite this, Arthur Eisen hired me as an Assistant Professor in 1986. Alice Pentland and I simultaneously set up independent laboratories across the hall from each other and we set off on parallel journeys. Janellen Smith and Christopher Zachary arrived from the University of Michigan at about that time and the four of us became good friends.

The next 3 years at Washington University were exciting and rewarding, but I was learning cutaneous immunology in isolation. Tom Lawley left the Dermatology Branch at the National Institutes of Health (NIH) to become Chair of Dermatology at Emory in 1988, and Steve Katz, then Chief of the Dermatology Branch and passing through as a visiting professor, decided that I would be a good fit. I arrived in Bethesda in 1989 and joined Steve, John Stanley, Wright Caughman, Peter Steinert, and Jay Robbins in the Dermatology Branch where I was immersed in skin immunology. The subsequent 27+ years at the NIH have been both professionally rewarding and personally enriching. My research program has been well supported by the National Cancer Institute (NCI) and I have been allowed to set my own priorities throughout my career. As my experience accumulated, I took on administrative responsibilities, initially as Dermatology Branch Chief and later as one of several Deputy Directors of NCI's Center for Cancer Research.

Over the years, I have benefited enormously from the close relationships that I have had with Branch Senior Staff members including those named previously and, in addition, those who came later and have since moved on. This latter group includes Andy Blauvelt, Sam Hwang, Tom Hornyak, Maria Turner, Emily Chu, Kim Yancey, and the late Jonathan Vogel. I continue to benefit from my almost daily interactions with current Branch Senior Staff (Isaac Brownell, Ed Cowen, John DiGiovanna, Heidi Kong, Ken Kraemer, and Keisuke (Chris) Nagao), most of whom I have recruited during my time as Branch Chief.

Successful scientists and mentors know that interactions with trainees are also incredibly influential. Laboratories in the Dermatology Branch are not silos, so I have developed close personal and professional relationships with fellows who I have supervised and mentored as well as fellows who have been supervised and mentored by others. An incomplete list of these talented individuals includes Alexander Enk, Setsuya Aiba, Neal Korman, Michael Hertl, Anne Bouloc, Andrea Cavani, George Elgart, Masayuki Amagai, Min Geol Lee, Teresa Borkowski, Kathy Schwarzenberger, Martin Roecken, Esther von Stebut, Rambi Cardones, Johann Bauer, Gunther Hofbauer, Zela Lazarova, Tom Darling, Sarolta Karpati, Thilo Jakob, Patty Walker, Tatsu Kawamura, Makoto Sugaya, Abel Lee, Edit Olaz, Hideo Asada, Keisuke (Chris) Nagao, Miklos Sardi, Brian Kim, Jan Gutermuth, Sei-ichiro Motegi, Yoichi Ogawa, Takeshi Ouchi, and Sohshi Morimura.

It can be anticipated that one will develop close relationships with coworkers and trainees. That I have also developed close relationships with individuals in other cities, states, and countries is amazing to me, in part because I think that few would describe me as a particularly social individual. Special relationships with Maria Morasso, Julie Segre, Stu Yuspa, Tom Lawley, Bob Swerlick, Georg Stingl, Kevin Cooper, Russ Hall, and Shinji Shimada can be attributed to shared membership in the extended NIH family. Other relationships are a testament to the welcoming nature of the dermatology and skin biology research communities and the unselfishness of the women and men that comprise it. I include relationships with the late Irwin Freedberg, John Olerud, John Voorhees, John Zone, Jon Hanifin, Luis Diaz, Erv Epstein, Robert Modlin, Dennis Roop, Bob Tigelaar, Paul Bergstresser, Akira Takashima, David Woodley, Janet Fairley, Joy Rico, Andrew Kowalczyck, Carien Niessen, Xiao Jing Wang, Dan Kaplan, and Kathy Green in this category.

Along the way, I have learned a few things (some the hard way) that approximate universal truths. It is great to be lucky. The potential impact of serendipity cannot be overestimated. Family is really important. Personal integrity is paramount. People cannot succeed if they are never given a chance. Proper training is essential, and shortcuts are not (usually) a good idea. Having the opportunity to be an independent investigator and/or a physician is a privilege. Mentors and environment are important at all stages in one's career. Mentoring is a two-way street. Finally, and as this editorial suggests, being a dermatologic researcher can be a very social experience.

We are particularly fortunate to belong to a vibrant global dermatology research community. It comprises many accessible, welcoming, and generous individuals who will go out of their way to be helpful, especially to young people. All one has to do is reach out. Those of us who are not “hard wired” to be extroverts may have to work at this a bit, but the payoffs are huge.

I will leave the Dermatology Branch at NCI to become Editor of the *JID*, effective 1 June 2017. In doing so, I will cease being an “active researcher,” but will I remain connected to scientific investigation, to dermatology research, and to the Society of Investigative Dermatology and the European Society for Dermatological Research. This editorial has emphasized the impact of personal relationships on me and my career, so you can appreciate that I feel privileged to be able to maintain these connections in my new role. I look forward to continued interactions with those of you who are already friends and colleagues, and to meeting others for the first time. Let us enjoy the journey, helping each other along the way" (157).

152. The contribution of genome mining strategies to the understanding of active principles of PGPR strains.

Pathogenic microorganisms and insects affecting plant health are a major and chronic threat to food production and the ecosystem worldwide. As agricultural production has intensified over the years, the use of agrochemicals has in turn increased. However, this extensive usage has had several detrimental effects, with a pervasive environmental impact and the emergence of pathogen resistance. In addition, there is an increasing tendency among consumers to give preference to pesticide-free food products. Biological control, through the employment of plant growth-promoting rhizobacteria (PGPR), is therefore considered a possible route to the reduction, even the elimination, of the use of agrochemicals. PGPR exert their beneficial influence by a multitude of mechanisms, often involving antibiotics and proteins, to defend the host plant against pathogens. To date, these key metabolites have been uncovered only by systematic investigation or by serendipity; their discovery has nevertheless been propelled by the genomic revolution of recent years, as increasing numbers of genomic studies have been integrated into this field, facilitating a holistic view of this topic and the rapid identification of ecologically important metabolites (158).

153. SIM Serendipity.

The pediatric emergency department (ED) was in the midst of its early morning ritual. There were no patients waiting to be seen. I wanted to help wake up the residents with a simulated pediatric code. As I set up our SIM Baby, I decided to simulate a respiratory arrest. This infant would be very sick and difficult to save.

As our faculty and residents filtered out of Morning Report, our clerk made the overhead call: *"Pediatric Code Pediatric ED, Pediatric Code Pediatric ED."*

Our response team came running: physicians, nurses, respiratory therapists, a clinical pharmacist, and ancillary staff. The momentary surprise, and relief, that it was a SIM case quickly transitioned into the serious clinical demands of responding to an infant on the brink of death. Tools were retrieved, commands were issued, medications were called for and administered. Team members worked while others observed. In the end, despite the team's best efforts, the SIM patient could not be rescued. Death was pronounced, there was a moment of silence, and a grieving mother was provided support.

The simulation and our clinical performance went, well, okay. It demonstrated that there were areas for improvement. As we debriefed, we talked openly and constructively about what we might have done differently. The discussion provided an opportunity to process not only the intricacies of a pediatric code but also our visceral responses to the death of a young child.

The debriefing engendered a sense of ownership, teamwork, and collaboration. We shared an experience that produced very real effects and emotions. Some team members verbalized being grateful for an opportunity to practice and learn this way, as simulation education is relatively new to our department. As we packed away the equipment, we sensed that our time had been well spent. There was a sense of appreciation.

It was probably a half hour later, although it seemed much less.

"Respiratory therapist to the ED stat" was heard overhead. My first thought was someone didn't get the message. The simulation was over. At that moment, a mass of people burst through the door with a pale and lethargic 13-month-old infant who was barely breathing. We could not have been more prepared.

The team showed up and jumped into action with a level of confidence and coordination that soothed the distraught parents at the bedside. The Broselow tape went down; the same tools and medications were now actually needed. The baby was intubated, resuscitated, and stabilized. There were some very harrowing moments but we kept to our algorithms. We kept our cool. The infant was stabilized.

The sense of accomplishment shared by the team was evident in our hugs, tears, and smiles. We shook our heads with grateful disbelief that we had practiced the simulated case minutes earlier. Our performance was obviously enhanced by the previous simulation.

Simulation education has evolved during the past decade in both technique and as a standardized tool for resident assessment. Simulation enhances cognitive and procedural skills and engenders confidence in those skills in a stress-free environment. The use of simulation education has been adapted by the ACGME in assessing core competency in resident training for the advancing emergency medicine resident. As per the SAEM's Simulation Task Force: "Medical simulation promises to revolutionize health care education, and emergency physicians are actively participating in the development of this field."

Every member of our ED team experienced the real and enduring benefit of simulation education that unforgettable morning.

By the way, our 13-month-old was extubated the next day and is doing fine! (159).

154. Intralipid for Amniotic Fluid Embolism (AFE)?

In 1998 it was first showed that intravenous Intralipid could prevent or improve resuscitation from cardiovascular collapse by severe bupivacaine overdose in rats. Since then published examples now include toxicities related to verapamil, diltiazem, amlodipine, quetiapine and sertraline, haldoperidol, lamotrigine, olanzapine, propranolol, atenolol, nevigolol, doxepin, dosulepin, imipramine, amitriptyline, glyosphate herbicide, flecainide, venlafaxine, moxidectin, and others. Amniotic fluid embolism (AFE) is a rare but potentially catastrophic obstetric emergency. Despite earlier recognition and aggressive treatment, morbidity and mortality rates remain high. An estimated 5% - 15%

of all maternal deaths in Western countries are due to AFE. The pathophysiology of AFE is not completely understood. AFE most commonly occurs during labor, delivery, or the immediate postpartum period. However, it has been reported to occur up to 48 h postpartum. Pulmonary hypertension and right heart strain/failure may be the result of physical amniotic fluid debris in the pulmonary vasculature or, perhaps more likely, result from circulating pulmonary vasoconstrictive mediators. Therapy with Intralipid in male rats resulted in 100% survival and prevented Pulmonary arterial hypertension-induced right ventricular failure by preserving right ventricular pressure and right ventricular ejection fraction and preventing right ventricular hypertrophy and lung remodeling. In preexisting severe Pulmonary arterial hypertension, Intralipid attenuated most lung and right ventricular abnormalities. The beneficial effects of Intralipid in Pulmonary arterial hypertension seem to result from the interplay of various factors, among which preservation and/or stimulation of angiogenesis, suppression and/or reversal of inflammation, fibrosis and hypertrophy, in both lung and right ventricular, appear to be major contributors. In conclusion, Intralipid not only prevents the development of Pulmonary arterial hypertension and right ventricular failure but also rescues preexisting severe Pulmonary arterial hypertension. Intralipid treatment is a new treatment for AFE (amniotic fluid embolism) which was never suggested before. Animal studies should be done in order to evaluate this new treatment modality (160).

155. Lipid Emulsion Rescue of Amniotic Fluid Embolism-Induced Cardiac Arrest: A Case Report. A&A Case Reports:

Amniotic fluid embolism (AFE) is a rare and often fatal complication that occurs in the peripartum period. We present a patient with an AFE who developed disseminated intravascular coagulation and cardiovascular collapse who may have benefitted from intravascular lipid emulsion rescue. This is the first published case in which lipid emulsion was a part of the successful treatment of AFE (161).

156. It was serendipitous

"Dr. Eldor,

I recall reviewing your article prior to publication. I have been interested in lipid emulsion since reading Dr. Weinberg's 12 dog study in the early 2000's and have published several manuscripts on the topic of lipid emulsion therapy

and have given regional talks on the topic as well. I have been very interested in how lipid emulsion may work in other drug toxicities as well as unique patient conditions. Your letter to the editor sparked an interest in AFE and I thought it was an interesting concept. I must admit that 2 of my associates were the primary caregivers for the patient in this report and I was called in on the case after the lipid emulsion was given. We had discussed your idea at a research meeting for our entire department and I had made the comment that, if I encountered a patient with AFE that was not responding to standard treatments, I would strongly consider using lipid emulsion. In the interim time, I had done a lot of literature searches on what exactly an AFE was and what the components of amniotic fluid were. The more I read, the more I thought that it may actually work (although, the more I read about the research in this area, the more I believe that it worked for very different reasons than the ones you and I likely thought it might work). My associate that made the decision to treat with lipid emulsion had not been present at our research meeting, so he gave it for a different reason. He gave it just in case he was missing something with regards to the neuraxial local anesthetic. When he informed me of the case, my mind immediately went to your theoretical scenario. My other colleague was doing a rescue TEE at the time of administration and was able to verify that the lipid emulsion was temporally related to a return of spontaneous circulation after 40 minutes of CPR/ACLS. As soon as my colleague told me about it, I said, this is what we talked about 3 (now ~5) years ago. So, you could say it was serendipitous without a doubt. Maybe not the way that you have described, but certainly in the fact that they were considering the possibility of different diagnoses.

- It was serendipitous that I happened upon Dr. Weinberg's research while thumbing through *Regional Anesthesia and Pain Medicine* and made our department early adopters of the LAST treatment protocol
- It was serendipitous that I signed up years ago to be on the editorial board of a new open journal of anesthesiology (I likely would have never seen your letter otherwise)
- It was serendipitous that I happened to receive your letter on the subject to review
- It was serendipitous that I did literature searches to further my understanding of AFE
- It was serendipitous that I mentioned it to colleagues at a departmental research meeting
- It was serendipitous that my colleague made the decision to give it, despite not having been there to hear my suggestion
- It was serendipitous that I was the first person he informed of the event (he came to me to praise one of our residents, the first author) for doing a great job (I am the program director)
- It was serendipitous that I recalled all that I had learned over the past 3 years on the subject and was able to go see the patient and connect the dots that they were struggling to understand (the chart review and personal accounts of events lined up perfectly)
- It was serendipitous that the patient had a relapse ~10 minutes after the first bolus, as its effects wore off (no infusion was started initially) and that the quick thinking team gave a second bolus that was witnessed to have a similar effect. This gave us further evidence that it was not just a fluke.

So, yes, I think there was a lot of “serendipity,” or divine intervention, or something that helped the excellent outcome to be possible. Something happened to put the right people in the right place and allowed them to make decisions that many would not have considered.

It is my hope that research and other case reports will confirm what we have suggested to be true with our case report. If so, many patients will benefit since the morbidity and mortality for this condition is so high. Since there are usually two patients affected, one patient saved could positively impact two lives (162).

Best regards,

Russell K. McAllister, M.D.
Residency Program Director
Assistant Dean-Quality & Patient Safety
Associate Professor of Anesthesiology
Texas A&M HSC COM / Baylor Scott & White Health"

Conclusion

Innovation is the engine of scientific progress. The tools are these: 1) finding the right question; 2) enhancing observation; 3) using analogies; 4) juggling induction and deduction; 5) changing your point of view; 6) broadening the perspective; 7) dissecting the problem; 8) leveraging serendipity and reversal; 9) reorganization and combination of ideas; 10) getting the most out of groups; and 11) breaking out of habitual expectations and frames (8). A healthy dose of serendipity is needed. Serendipity Based Medicine (SBM) is a new definition for an old engine of medicine that can bring results to infinity and beyond. Serendipity is an important theme in medical innovation. There is no reason to think this will change. Things do not necessarily go as planned, but often the results are as important as the original prediction was supposed to be. It will not be clear where we end up until we get there.

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