

## On the Exploitation of Serendipity in Drug Discovery

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We have written previously about the nature of serendipity and the role that it played in the “Psychopharmacology Revolution” of the 1950s and 1960s [1-3]. However, we have not previously addressed the issue of whether it is possible or desirable to design studies to enhance and exploit serendipity. We do so here.

First, it is essential to establish a definition of serendipity. As we suggested previously [1], the term serendipity shall be defined as “the discovery of something not sought”. This definition, like most others, requires the element of sagacity. The observation of “something not sought” will not lead to discovery unless someone has the mental discernment (sagacity) required to recognize that the observation has significance. However, sagacity cannot be used to differentiate serendipitous from non-serendipitous discoveries because it is a necessary attribute of both. Sagacity and discovery are synonyms in this context.

Most definitions of serendipity require the element of chance. Indeed, discussions of serendipity invariably quote Pasteur’s famous dictum “Chance favors the prepared mind” [4]. Whether chance is a feature of serendipity depends on one’s definition of chance. A common definition of chance treats the word as a synonym for random. Thus, Dictionary.com defines chance as “the absence of any cause of events that can be predicted, understood, or controlled” [5]. The Free Dictionary defines chance as “The unknown and unpredictable element in happenings that seems to have no assignable cause” [6]. If this meaning of chance is a required element of serendipity then the construct of serendipity is rendered non-scientific, for certainly science can only explain events that have causes. Another way to define chance is “something that happens unpredictably without discernible human intention...” [7]. Here chance is treated as mere coincidence. There is nothing scientifically objectionable to this definition. However, when used in this way, chance is equivalent to the phrase “something not sought”.

Most experts in psychopharmacology would agree that, by comparison to the period referred to above as the “Psychopharmacology Revolution” [8], the pace of discovery of novel psycho-pharmaceuticals in recent years has been relatively anemic. It is critically important to identify factors that may now stifle drug development. At least one prominent expert has attributed the apparent stagnation to a decline in serendipity [9]. Indeed, many commentators, us included [1-3], have observed that serendipity played a pronounced role in the discoveries of the earlier period.

Several putative “anti-serendipity” factors that may interfere with current drug development have been identified. These include 1) movement toward rational drug design based on translational research, 2) reduction in the amount of time that clinicians have to observe patients, and 3) reliance on the double-blind placebo control design to demonstrate efficacy [9].

The trend toward rational drug design is clear [10]. However, its relationship to serendipity is opaque. Rational drug design guided by translational research refers to the development of drugs deliberately designed to alter processes that have been implicated in mental pathology by basic research. Rational drug design, by its very nature,

constricts the domain of drugs of interest by singling out for clinical trial only those compounds that basic research and theory suggest may alter the mechanisms of psychopathology. Modern techniques enable rapid development and screening of thousands of compounds designed for activity at specific molecular or cellular targets. In the past, selection of drugs for clinical trials was based primarily on coincidental or deliberate observations of drug effects on the behavior of animals or humans. Thus, in a sense, early drug development was rational too. The difference between then and now is that now drugs must pass through a molecular/cellular screen before they are selected for molar physiologic, behavioral or clinical trials. If there has been a constriction of serendipity due to rational drug development, the impact of the effect is exerted at the initial phases of drug development and it is due to homogenization of the physico-chemical properties of agents that pass through the screen, thereby reducing both the variability of the biological effects of these compounds and the probability that “something not sought” will occur and be recognized. Constriction of serendipity is not an inherent aspect of rational drug design. Rather it is the consequence of theory. Screening of drugs designed to test different theories of the pathogenesis of mental illness would broaden the variability of biological effects and enhance the probability that “something not sought” will occur.

Another putative “anti-serendipity” factor is a constriction in the amount of time that clinical researchers have to observe drug effects. Interestingly, this has been linked to the closing of long-term care mental hospitals (i.e., deinstitutionalization) [9]. Several points are relevant here. First, testing of drugs that target severe mental illness, such as antipsychotics, is still often done in a hospital setting (see, for example [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/97/20639\\_seroquel\\_toc.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20639_seroquel_toc.cfm)). Second, long-term observation is not usually required to observe therapeutic effects. The efficacy of most psychiatric medications is demonstrable within a few weeks or less. Typical phase III clinical trials last for six to eight weeks and involve hundreds to thousands of participants [10]. Often rating scales are used to measure drug effects. Reliance on rating scales, as a substitute for longitudinal clinical observation, has been suggested to be another “anti-serendipity” factor [9]. However, the most commonly used rating scale, the Brief Psychiatric Rating Scale (BPRS), samples a broad range of symptom categories including somatic concern, anxiety, depression, suicidality, guilt, hostility, elevated mood, grandiosity, suspiciousness, hallucinations, unusual thought contentment, bizarre behavior, self-

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neglect, disorientation, conceptual disorganization, blunted affect, emotional withdrawal, motor retardation, tension, uncooperativeness, excitement, distractibility, motor hyperactivity and mannerisms and posturing [11]. Indeed, the BPRS is not so brief. Thus, the duration of modern clinical trials and the breadth of symptoms examined appear to provide ample opportunity for the observation of “something not sought”.

Another putative “anti-serendipity” factor is the use of the double-blind placebo control design [9]. The principal objection to this design is that the design does not allow for analysis of individual differences in drug response. This is accurate. Outcome is expressed as a group average, and idiosyncratic responses are relegated to the status of background “noise” or error. Behavioral psychologists have vociferously complained about this for more than half a century, advocating the use of single subject designs (n=1) as an adjunct group designs [12]. Use of such designs in psychopharmacology would be fruitful in identifying individual response markers. However, single subject designs are rarely used in clinical drug trials. No doubt, this is because drug developers are more interested in drugs that have more or less uniform effects across a large number (group) of subjects (and potential customers), than identifying idiosyncratic effects in individual (n=1) subjects. However, the group design, rather than being an “anti-serendipity” factor, actually increases the odds of producing “something not sought” because of the inherent variability between subjects within groups. Single subject design would not promote serendipity per se. Rather, it provides a means for exploiting serendipitous observations by enabling researchers to understand why drug effects vary across individuals within groups, and in doing so, it would probably help to reveal multiple pathologies that are at present lumped together under single diagnostic categories.

Our analysis suggests that the current lack of innovation is not due to suppression of serendipity. What, then, is? The current bureaucratic requirements that must be satisfied before a new drug can be brought to market cost about 80 to 100 million dollars and require, on average, ten years reaching fruition [10]. The high costs in time and money create tremendous pressure on drug companies to reduce the risk that a drug selected for development will not be approved. A pervasive strategy for enhancing success in drug development is to develop drugs that are similar to those already been approved and are clinically successful. The result has been the marketing of multiple drugs that are virtually equivalent in mechanism of action and efficacy. There is much greater financial incentive for the development of so called “me too” drugs than novel compounds. This is a primary obstacle to innovation. The constriction in the diversity of compounds selected for clinical trial that is inherent in this approach reduces the range of possible outcomes and reduces the probability of discovering something “not sought”. Nevertheless, the system is not fundamentally “anti-serendipity”. A drug company that observes an unexpected but clinically useful and profitable effect of a drug in the course of testing it for something else will not care whether the discovery was made by accident during intentional development of “me too” drugs. The drug will be developed for the use “not sought”. For example, the effect of Viagra® (sildenafil) on penile erection was discovered during the testing of phosphodiesterase inhibitors for treatment of angina [13].

It has recently been suggested that serendipity is a “proven method” of science and that research designed to promote serendipity would stimulate innovation in drug development [9]. In the discussion above, we suggest that the probability of a serendipitous observation is related to variability in compounds tested, end points measured, and the time allocated to observe effects. A plausible case can be made that there has been a constriction in the range of compounds tested. This is driven by two forces - rational drug design and risk adversity. Rational drug design is synonymous with theory driven research. Retreat from theory driven research in order to promote serendipity would be a scientific regression. It would represent a retreat toward irrationality and the trial and error approach of the past. Regarding the range of outcome variables measured and the time allocated to observed effects, it is debatable whether these variables have actually been constricted. We agree that the pace of discovery of more efficacious drugs for the treatment of mental disorders in recent years has been relative slow. However, we attribute this to powerful economic incentives that promote the development of drugs that have mechanisms of action similar to drugs already on the market. Enhancing serendipity is not the remedy for the stagnation of drug development. Rather, the solution lies in increased testing of novel theories and compounds. This solution is antithetical to the entrepreneurial, private-sector, profit-motive approach that drives most drug development. Herein lie an exemplary role for government-supported research aimed at testing novel theories and compounds without regard to the bottom line.

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