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Commentary

At the intersection of systematic and seismic: examining the way forward for pediatric research

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In 1962 the physicist philosopher, Kuhn, published the *Structure of Scientific Revolutions*. He described what he called "normal science" research based upon past scientific achievements that is "puzzle-solving" and "incremental"; it is often a way to clean up the status quo. Only when data anomalies are detected do new paradigms emerge. Kuhn challenged the view that "normal science" leads to progress. Instead, he posited that normal science is interrupted by periods of revolutionary science. This is how we move past "puzzle-solving," where there are typically preset rules and solutions, and arrive at novelty and invention.

However, what is the status quo and how is it established? Kuhn called these constructs of how we view science and ask questions, "paradigms." These paradigms guide our path to discovery and our perspective on our interpretation. Kuhn stated that "no natural history can be interpreted in the absence of at least some implicit body of intertwined theoretical and methodological belief that permits selection, evaluation, and criticism." (1) Paradigms are self-reinforcing, as they often define what questions we ask and are necessary for research questions to be posed in a systematic, theoretically sound manner. There are five key steps to establish a paradigm: (i) a random collection of facts emerge; (ii) pre-paradigmatic structures are created; (iii) one paradigm emerges that seems better than the others, but still allows room for further discovery; (iv) the emerging paradigm inspires a new generation of scientists; and (v) a discipline that binds this way of thinking and conducting science emerges, transforming a group into a profession. However, along the way yesterday's paradigm becomes today's status quo.

The classic scientific discovery paradigm is illustrated by the remarkable story of Stanley Cohen. In 1986, Dr Cohen was awarded a Nobel Prize for the discovery of epidermal growth factor (EGF). He discovered this by noticing that rats in his experiments that received extracts from male mice salivary glands opened their eyes earlier. This astute observation led to his discovery. The discovery of EGF was key to understanding how cells proliferate rapidly. This became especially important for cancer cells and paved the way to develop anticancer agents. Did Dr Cohen set out to discover anticancer agents? No, he applied a rigorous curiosity and scientific methodology to meticulously test his hypotheses. It took him decades to conduct this work, during which time he changed his research questions, his research design, and failed multiple experiments. His story is a great success story of a classic systematic research method applied over decades, resulting in discoveries that change how we treat a disease, in this case, cancer.

I posit that today we live in a world where our paradigm of systematic, time-intensive, iterative approach to scientific discovery seems to be at odds with the rapid pace of a world that contextually functions differently because of the exponential increase in information, technology, and each other. What are the emerging new discovery paradigms and what is our responsibility as scientists at this intersection between systematic and seismic?

What creates this seismic context? Consider that in 1900 it took 100 years for knowledge to double, in 1945 it took 25 years, and today it is thought to take about 13 months. The pace of information and our access to it outstrip our capacity to utilize it in our current research paradigms. Therefore, new discovery paradigms in how we both ask and answer scientific questions are emerging. Below, are five examples.

1. Access to our genetic code: CRISPR-cas9 clustered regularly interspersed short palindromic repeats, is an RNA-guided genome-editing tool to target loci and generate site-specific double-stranded breaks. This has promise for treating monogenic disease such as Duchenne Muscular Dystrophy. For example, in rodent models, targeting the introns 22 and 23 of the *dmd* gene removes the disease-causing mutation, resulting in a restoration of dystrophin expression and muscle function. However, it is yet to be determined how this can and will be translated to humans, and things such as off-target effects, efficacy, specificity, and immunogenicity need to be addressed (2). Access to our genetic code pushes us inexorably forward toward a new paradigm where we could envision eradicating some conditions and diseases that previously were thought incurable.
2. Access to new technology: the National Research Council defines precision medicine as "the tailoring of medical treatment to the individual characteristics of each patient." Although the name implies accuracy, the

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science of precision medicine will require a greater capacity to calculate and interpret probabilities. Vermaat *et al.* (3) posit that from the 1950s to recently we have been in a state of divergence, exponentially increasing scientific knowledge and identifying targetable pathways. Now we are in the state of convergence, integrating the data generated, developing a probability formula, and determining how to apply that to individual patients in a tailored manner. Already some medical institutions are identifying one's genetics to guide medical therapy and reduce potential side effects at point of service in the clinical setting. For example, genetic testing of the highly variable cytochrome P450 2D6 drug metabolism enzyme has been used to tailor codeine use for patients with sickle cell disease. Whereas in the past translation of medical discoveries has, on average, taken the scientific and medical community an average of 17 years, access to "big data" such as that found in the medical record plus individual whole-genome data and other sociocultural determinants of health pushes us toward a paradigm where real-time discovery could get quickly integrated into clinical care.

3. Access to new methods: the story of induced pluripotent stem cells (iPSCs) started almost 60 years ago; however, about a decade ago, Yamanaka demonstrated direct reprogramming of somatic cells without the need for nuclear transfer (4). Patient-derived samples of iPSCs can be used to develop patient-specific disease models, allowing us to better understand both the mechanism of disease and new therapeutic approaches. This already affects our approach to regenerative medicine for some types of transplantation, but it could also expand to how we regenerate heart and brain cells after ischemic events or how we treat neurodegenerative conditions. However, there is still much to be done before this method can begin saving patients' lives. With this remarkable potential also comes the challenges of inducing cancer and a potential disruption of immunological homeostasis (5). Therefore, while this new paradigm emerges, it is imperative that the scientific community develops and implements processes to determine when and how these new methods should be used.
4. Access to each other: an emerging paradigm is our ability to share real-time data, as quickly as possible when an epidemic is most vulnerable to intervention. This approach can include laboratory, epidemiologic, and behavioral data. To curb outbreaks such as this, speed of research to effective application is critical. When the Zika outbreak was reported, using social media platforms an international group of researchers accessed data in real-time to identify the spread, contain it, and begin work on pharmacologic and immunologic treatments (6). Developing global processes and standardized protocols to support this type of coordinated rapid response to public health outbreaks is an emerging new paradigm. In February 2016, the statement of data sharing in public health emergencies was issued. Research infrastructure needs to evolve to both respond to these emergent situations and allow for alignment of academic advancement.
5. Access to multigenerational information: the Barker hypothesis in 1990 suggested that early exposures in life affected whether we would go on to have a disease later in life. For example, rapid weight gain between the ages of 2 and 12 was more predictive of adult obesity than BMI at any one age and this was correlated with later coronary artery disease in adulthood. This concept of how we carry our early exposures within our pathophysiology is not new, but our enhanced capacity to link to multiple generational data is. Our technologic advancements now allow us to examine disease and health through a multigenerational lens, changing our paradigm from "right now" to "throughout the generations."

These discovery paradigm shifts push us to restructure how we ask and answer questions and meet society's voracious appetite for timely scientific discovery. Our foundational model of systematic, deliberate, iterative, with many opportunities to fail until we succeed, on which our academic infrastructure was created, now meets society's expectations that research needs to be efficient, cost-effective, translatable, and utilize existing resources whenever possible. Therefore, at the intersection of systematic and seismic, we need to ask ourselves these questions:

1. In this fast-paced world of exponential information, how do we separate information from knowledge?
2. Given the expectation of a faster pace of scientific discovery, how can we ensure validity of our findings before translating the results into new knowledge?
3. How will this change our research infrastructure to respond to today's changing context?
4. How will all these new expensive approaches be funded and what are the trade-offs?

For this is what we do when we are at an intersection, we look all ways and then determine the way forward.

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