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"Fickleness" in Biological Systems - Really?

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Commentary

In several news articles in SCIENCE [1] authors reported on the responses of many scientists regarding the irreproducibility of studies in biomedical research, especially cancer biology. The common concerns were "problematic reagents and the fickleness of biological systems". NATURE continued capturing data on the problem of non-reproducibility, noting that the biomedical science has more non-reproducibility problems than physics, chemistry, and mathematics [2].

Biological variability or "fickleness" is considered by many to be an inherent property that is uncontrollable. This, therefore, leads to major difficulty in reproducing experimental results in the biomedical sciences.

Much of the variability (fickleness) found in research on biological systems, is easy to control if one appreciates the statistically significant fluctuations in all biological variables that occur naturally and reproducibly every day. Without controlling for these normal, significant oscillations, different results will be obtained by different groups of researchers. For example, studying the effect of isoproterenol (IPR) on the rate of DNA synthesis in different mouse organs involved repeating the same experiment at different circadian times, such as every 4 hours (same for the saline treated controls) in different groups of mice [3]. In other words the only variable changing was body clock time. Three different statistically significant conclusions were obtained: IPR stimulated, had no effect or inhibited the rate of DNA synthesis. Which of these results were correct? Actually of them, they just vary depending on the point in the host's circadian clock system when the intervention occurred. Without an experimental design that controls for circadian variation, the effects of IPR would be irreproducible. Completely different results are a common finding in chronobiological investigations when control treated mice are matched in circadian time to the interventional group and multiple circadian time points are included in the experimental design.

SCIENCE listed research on the biological clock in its top ten list of discoveries of major importance in 1997 [4] and again in 1998 [5], when clock research was first runner-up. This official recognition of the importance of biological rhythmicity 20 years ago apparently has not been heeded by the majority of basic and clinical researcher, leading to non-reproducibility of experimental findings published by different research groups.

There are a variety of pitfalls that researchers fail to control for in biological research on systems that normally and naturally undergo significant oscillation or rhythmicity [6]. In other words, without knowledge of biological rhythmicity as a characteristic of all living things, and not controlling for this natural, statistically significant variability, and the effect this has on experimental design, data acquisition and interpretation, reproducibility is impossible.

With respect to "The Cancer Test" and the problem of non-reproducibility in such an important arena, enough basic animal research in chronobiology, chronotoxicology, chronopharmacology and chronochemotherapy of cancer [7-11], that several successful clinical trials of chronochemotherapy in the human cancer patient have been, as predicted by earlier work with mice, very successful [12-14]. These findings would be reproducible if the dimension of time was appreciated and incorporated in these investigations.

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