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Review

# The answer is not 42

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ABSTRACT

During his long and illustrious career that now spans over 50 years David Triggle has had a major impact on biomedical science that can be linked to his research spanning the disciplines of chemistry and biology. Capitalizing on his undergraduate and postgraduate education in chemistry David's early research explored the pharmacology of adreno- and muscarinic receptors ultimately leading to studies of the cellular signaling processes that mediated the effects of receptor activation particularly with respect to calcium homeostasis. David's contributions to the identification and development of calcium channel antagonists resulted in benefits beyond the impact of such drugs in the treatment of diseases of the cardiovascular system. During David's 50+ year career many technological changes have occurred that have affected how research is conducted, funded and published and how its impact evaluated. Not all of these technological advances are necessarily positive and it is valuable to reflect on the long lasting impact of David's accomplishments with reference to such changes.



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## 1. Introduction—a bit of history

David Triggle's first publication appeared in the Journal of Medicinal Pharmaceutical Chemistry (now Journal of Medicinal Chemistry) in 1962 with the title: *"Blockade of adrenergic alpha-receptors by a carbonium ion"* [1]. This paper, which has been cited 30 times, describes the chemical basis for the alkylation and non-competitive inhibition by β-haloalkylamines of α-adrenoceptors. At the time that this research was being performed, 1959–1961, David was a National Research Council of Canada postdoctoral fellow working with Professor Bernard Belleau, a Canadian molecular pharmacologist, who at that time was Professor of Chemistry at the University of Ottawa and the co-author on the paper with David. Professor Belleau moved to McGill University in Montreal in 1971 and was one of the co-founders of the Montreal-

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based company, BioChem Pharma that was responsible for the development of the anti-AIDS drugs 2,3 dideoxy—3-thiacytidine (3TC) and lamivudine that have greatly benefited the life expectancy and quality of life of patients with HIV (human immunodeficiency virus) and HBV (hepatitis B virus) infections. Of interest is that another author in this Festschrift, Gordon Bolger, also worked with Professor Belleau before moving to Buffalo and joining David's laboratory as a Ph.D. student in Buffalo.

David continued to pursue his interests in receptor pharmacology when he joined the Department of Biochemical Pharmacology at the State University of New York at Buffalo (SUNYAB) in 1962. Work with the β-haloalkylamines continued as David's research explored the pharmacology of both adreno- and muscarinic-receptors and their cell signaling mechanisms in smooth muscle. These studies ultimately led to the exploration of the ubiquitous role of calcium and calcium channels in the regulation of smooth muscle function and major contributions to the discovery and development of calcium channel antagonists. In parallel the story with β-haloalkylamines continued and a study published in1984 [2] described the effects of the β-haloalkylamine, phenoxybenzamine, on agonist responses on the muscarinic receptor in the guinea pig ileal longitudinal muscle suggesting that the inhibitory effects of phenoxybenzamine were being mediated in part by effects on the L-type calcium channel.

## 2. Fifty-three years of contributions to biomedical research

Jumping forward 53 years from his first publication in 1962 David Triggle now has a total of 245 entries in PubMed; however that number does not include several books and monographs or cited abstracts. A review of Web of Science entries for David reveals that the total number of citations from 394 captured publications (includes cited abstracts, monographs, books), but excluding self-citations, exceeds 9000 and 29 of his publications have achieved "classic" status—namely >100 citations and an *"h-index"* of 54 achieved. The *"h-index"*, or Hirsch index, was suggested [3] by the physicist, Jorge Hirsch in 2005, as a measure of the impact of a scientist in the published literature in his/her field. The *h* reflects the number of papers published *h* papers that have cited in other papers at least *h* times. Thus for David that equates to 54 papers that have been cited at least 54 times; however, the average number of citations for each of David's publications is approximately 30. David's productivity and impact was at its highest in the 1980s with 30 publications in 1984 and 600 citations in 1987. It should be noted that the actual number of citations might vary when comparing Web of Science with ResearchGate with Google Scholar.

## 3. Metrics

By any standard reviewing David Triggle's contributions to the scientific literature provides an excellent reflection on a very impressive career and it is interesting to look at how some of these publications have impacted the field. Other contributors to this Festschrift have also emphasized the impact that David has had not only on science, but also on their careers. First, though it is necessary to reflect on just how much the landscape has changed in the past 50 years with respect to the publication of scientific knowledge and how it's impact is measured. I will address the question: *"Are we today becoming too obsessed with metrics as a measure of the quality of science and too focused on whether the paper is published in a so-called high impact journal"*? I will argue that it is very difficult to objectively assess the true quality of a journal and apply an accurate numerical value, but, nonetheless, scientists today are essentially required to publish in the highest impact journals in order to advance their career and/or obtain research funds. In this regard I am certainly not the first to criticize such over interpretation of the meaning of "impact factor" [4] but the provision of metrics to one's publications seems to be far more important today than it was 50 years ago and along with that comes concerns on whether such an over emphasis on numbers is harming science. For the young scientist today "good metrics" is essential for obtaining a job and for older academic scientists "good metrics" is essential for obtaining and maintaining research funding and hence the frequently stated "publish or perish". But what really is "good metrics"? Furthermore, has the arrival of the digital age impacted on which measures are the most important for the quantification of "scientific impact"? Should we blame Lord Kelvin for after all it was he who impressed us with the need to provide numerical values? Quote: *"When you can measure what you are speaking about, and express it in numbers, you know something about it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts advanced to the stage of science."* [5].

Of significance, in 2015 the Royal Society celebrates the 350th anniversary of *Philosophical Transactions*, which is generally considered to be the world's first science journal. Furthermore, in April and May of 2015 The Royal Society held a series of meeting to discuss the following topics: peer review; the use of impact metrics in research assessment; reproducibility; ethics and misconduct; business models and profiting from publishing, and the mechanisms by which scientific knowledge is disseminated and assessed. We look forward to reading the results of these meetings, but the topics identified by the Royal Society are also those that I will touch upon in this article and indeed were central to an invited review article David and I wrote in 2007 [6]: "*What is the future of peer review? Why is there fraud in science? Is plagiarism out of control? Why do scientists do bad things? Is it all a case of: "all that is necessary for the triumph of evil is that good men do nothing?"* Although we discussed our concerns about the peer review process we did note that, in principle, peer review was necessary for quality control and others agree [7]. Unfortunately quality is not always fairly delivered and I am sure that many of us can provide examples of receiving shoddy reviews that seemingly have been completed in a hurry and bear no relationship to the manuscript submitted. Or, something like the one line review for a grant application of mine some years ago: *"My gut feeling is that this will not work"*—NOT exactly useful feedback to help with a revised submission! We also raised our doubts about anonymity of the peer review process, but, again, recognized that it was necessary to ensure the availability and willingness of reviewers to contribute. Negative bias and cronyism are also concerns as is the not infrequent lack of correlation between the recommendations of the reviewers [8]. Some have even debated the question of whether peer review is a form of censorship [9]. The difficulty in publishing so-called negative data was another concern as such data may, indeed, be very valuable particularly as today we see an increasing concern over reproducibility of data, or rather lack thereof, as well as false positive findings [10]. The lack of reproducibility of pre-clinical research has received considerable attention and is another cause of considerable concern [11,12]. There are likely many reasons for this lack of reproducibility: methodology and protocol design; inappropriate analysis; problems with reagents, notably antibodies and also cell lines and, unfortunately, fraud. The unreliability of some antibodies and origins of cell lines have both been recently highlighted [13,14,15]. One analysis suggests the percentage of irreproducible studies exceeds 50% and effectively wastes $28.0 billion USD/year [16]. Recognizing the value of negative data [17,18] is important if for no other reason than minimizing other researchers wasting valuable resources by attempting duplication of the same, but unpublished, study. We also questioned whether