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scientific communication-from traditional to modern journalism

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My goal in Neuroscience journalism was to change the format of traditional scientific journals, not by replacing them but by offering a new format for peer reviewed works to also run within. It is imperative in this case that the distinction be noted. *Stem Cells and Development*, a Journal which I founded, never ran as a report any paper that was not subject to peer review. But we did commentaries and other features that were not peer reviewed. Regarding patient accounts, I haven't reached any opinion regarding their standing in a peer reviewed journal. That being said, I do think patients' own accounting would be quite valuable to practicing physicians, and this endpoint is the goal many high profiles journals were founded to highlight.

Since the inception of scientific journalism, there have been serious flaws inherent in the system that have not been mitigated and in many cases aggravated as journalism evolved. Initially, journals were edited by one person. That person was the editor and the reviewer of most of the submissions. If a paper was submitted that was out of his or her scope, it would then, and only then be sent to a colleague for review. In those days, little thought was given to the profit the report may generate. Investigators were more concerned with acknowledgment of being first than they were with profit. However, patents were considered more important than copyrights, even as most modern nations agreed on laws governing both. However, it was quite easy to change the date of a journal (delivered by horse and wagon after being shipped on a steam ship to a city past the seaport at which it arrived), or should I assert, simply print a journal dated January 1, 1854 in June. This could not be done with patents, which was basically the situation that put Albert Einstein in an excellent position to learn first of scientific advances in the Physics of transmission of light, after twice being rejected for entry to graduate school because he was unable to either understand or pass math, even after studying for 2 years with a private tutor.

It is my understanding that at that time, most fields of Science held one, perhaps two journals in high esteem. If your paper didn't land in that journal (for Physics it was *Acta Physica*), it may just as well have landed in the trash can. Before Marie Curie told him why, Henri Becquerel published that waves, called radio waves, emitted from a rock rich in an element known as radon traversed black paper and developed the film shielded by the paper. This phenomenon initially upset him. Dr Becquerel was a fluorescent chemist and found that his small quantity of radon, purified from a raw extract of "pitchblende" (a substance mined in South Africa by workers paid by the government of Australia; I have no idea what they purified from it; they certainly were not making nuclear bombs) did in fact glow in the dark and the glow diminished rather rapidly as time progressed (even though the half life of radon was quite long). Madam Curie, who received her first Nobel with her mentor, Dr Becquerel before she received her doctorate, quickly showed Henry that the diminishing glow was not a result of diminished traditional fluorescence, another problem with tradition. She merely held the radon under a stream of running water and the glow resumed. What was readily apparent to her, perhaps the most brilliant person ever born, was that as the radioactive substance decayed, it degenerated into a product that blocked the light emitted from the rock, rendering the glow less bright. Prior to her doctoral thesis, she would describe the complete decay scheme for radon, which has about 49 steps, and would dismiss 17 (seventeen) other publications that claimed to show emission of waves from substances that passed through black paper developing the film below. Seventeen false papers, each fueled by the discovery of radio waves and eagerly accepted by the scientific community who held no doubt as to the veracity of the results. Since radiowaves could easily traverse bricks and mortar, as well as the soil of the earth, there was no question that they could

traverse a thin sheet of paper. But even while they could, they did not develop the photographic film below, which is rather easily exposed "inadvertently". To develop the photographic emulsion, the waves must be ionizing; a feature once discovered was termed to constitute radioactivity. Here is a vivid example of a result many eagerly anticipated and expected; a result which easily sold to several journals and did so after review of very critical reviewers. And each one was shown to be wrong, except for Curies' and Henri's report on radon.

While there is much more to this fascinating story, it serves as irrefutable early evidence that stringent peer review does not provide any means to avoid erroneous conclusions. Indeed, the award of the patent for discovery of "the ether", a substance said to pervade the universe and provide a substance for light and other EMWs to transmit through otherwise empty space was granted by Mr. Einstein, even while he was putting together an alternative interpretation of the meticulous results of Drs Michelson and Morey of Case Western Reserve University, who timed the speed of light emitted from a lantern placed on a raft supported by a pool of Mercury on a craft on Lake Eire and spun to either parallel to or opposite of the direction of the revolvment of the earth.

But what is even more important is the fact that Einstein's interpretation, which we refer to as special relativity, was published as a lead article in *Acta Physica* (and really, in Physics, if you didn't get the lead, again you were merely filling space) was not subject to peer review. If it was, it would have been blown to bits. Imagine, here we had a graduate school reject saying that as you go faster, you age slower, get smaller and live longer. The public was captivated, and Albert Einstein played the press brilliantly. He also may have facilitated the patent granted to Michelson and Morey to gain their alliance (which he did; he never once said they were wrong and praised their work at

every juncture; indeed it was defining, as their data were correct; it just depended on how you looked at it. Relativity by its own tenants cannot be proven; a theory it shall always remain. And of course, Jonas Salk decided to bypass peer review instead taking his findings to the Pittsburgh Press on April 24th, 1954, which scrubbed the printed edition for that day instead running under the headline "POLIO CURED" the trials and tribulations of Dr Salk. Had he sent his findings to the Journal of Virology, they would have been both reviewed and just perhaps delayed by his mentor, Dr Sabin, who was second, as Dr Salk was barred from NIH funding for life, membership in the Academy of Sciences and other awards. Funded by millionaires in Pittsburgh, he went on to found the Salk institute where investigators are barred from the delays incumbent in grant preparation.

The concept of peer review is hopelessly flawed and it is so in many important ways. Traditional journalism is ready for a change. The problem becomes more evident as science merges with "for profit" industry and peers are looking at factors that transcend their duty to evaluate the scientific merits of a manuscript. At its worse, peer review allows reviewers to delay publication while they reproduce the results and lay claim to the discoveries, a problem that has existed for years. Peers now must also evaluate how acceptance or denial impacts profit margins. But those who strongly endorse peer review are those who both set the rules and who are in the best position to profit from the rules as set and as they evolve. I still do not understand the problem of going public prior to publication; why is this disdained. It is because it avoids allowing reviewers to always have the final say, I submit. The traditions of journalism have not changed as quickly as the traditions of science, and they should. To date, traditional journalism has allowed the unhindered dissemination of false hope and unproven assumptions many of which had about reached the point of "dogma"; and then along came *Stem Cells and Development*, a Journal dedicated to holding this dogma, aggressively disseminated by

willing publishers to an avid audience consisting of both lay individuals, the lay media and scientists. No one held to question the report run in *Nature* that claimed to "Turn Blood into Brain". A few question post-natal transdifferentiation in mammals, yet the evidence that this in fact occurs is scant. Very few question "cloning", but I for one am not so sure.

Stem cells were held to be the magic bullet for most diseases known to man, particularly diseases of aging, and a few if any questioned the very concept, the concept of a singular pluripotential stem cell which held, based on thin data derived from the hematopoietic system, the ability to regenerate an entire organ system from a single cell and do so therapeutically. No one questions the fact that we are all derived from a single cell; the fact that a single cell supposedly could restore hematopoiesis in a marrow ablated mouse led to the premature conclusion that a similar cell would be available to regenerate all organs in their vast complexity. The single cell genesis of the definite hematopoietic system is a theory that when proposed was not readily accepted. It should still be held to strict question. In any event, as I recently wrote with Drs Gluck, Anand and Verma, the methods used to effect successful hematopoietic cell engraftment are not those used with MSC's, which to date have not resulted in regeneration of any organ, and the concept of transdifferentiation is very tenuous after fetal development. I do not believe it can be induced; all results reported to date can easily be ascribed to fusion and contamination of the starting material, adherent and culture expanded hematopoietic "precursors" do not hold the ability to restore hematopoiesis. Indeed, cultured myeloid progenitors do not have the ability to cure neutropenia and erythroid progenitors do not hold the ability to reverse anemia. The entire marrow has to be replaced. In the paper I sent regarding transplants of chondrocytes as a cure for osteoarthritis, I carefully point out that after 20 years of trying, no success has been achieved.

This is a good model to explore the question; why not? The MSCs used almost

by default differentiate to chondrocytes in culture. Tagged, it is evident that these progenitors migrate to affected joints of patients with osteoarthritis, joints whose pathology is characterized by one single defect; lack of chondrocytes. It would seem, based on what almost became dogma that a MSC transplant would certainly be curative in patients lacking a single cell if this cell reaches the target and it does. In many studies, chondrocytes were injected directly into affected joints; in others, chondrocytes were incorporated into collagen mixtures such as alloderm and injected into affected joints. The sum of the hundreds of clinical trials showed only one common consequence; the transplant either had no lasting effect or worsened the pathology, resulting in hyperplastic proliferation of chondrocytes, premature ossification and joint destruction. This result has been summarized in strictly reviewed papers I cited and cannot be held to question. A way should be found to reach success in chondrocytic transplants, but we haven't even scratched the surface. The use of methods that actually cause marrow stem cells to fail to engraft (culturing them) is curious as marrow transplantation is used as the proof of concept.

Having said this, let me stress that this is but the tip of the iceberg. Traditional journals are not going to perish and I have no desire that they do. I just want it to be known that factors other than science now impinge upon reviewer's concerns and actions. One factor leading me to step down from *Stem Cells and Development* is that a prominent stem cell scientist went over my head and contacted the publisher of the journal who assured him of the impending acceptance of his paper even as I prepared the rejection letter and even as I was thinking of ways to avoid even having to evaluate papers from for profit firms. But let me cite one example; the CEO -- usually a scientist who started the concern based on a need he hypothesized his research would fulfill-- hires 10 techs and has them working on aspects of his hypothesis. These individuals are well aware of the fact that their continued employment depends on the continued

existence of the firm which depends on the hypothesis being validated in the lab. Specific experiments are sent to the techs by the boss and his or her assistants. It does not take a neurosurgeon (perhaps a rocket scientist) to guess that the results by and large are going to be consistent with the hypothesis on the table; it is human nature, perfectly understandable and when discovered, hardly an unusual finding any more which presents a big problem. Our NIH went to great lengths starting with President Reagan to meld Business and Basic research; the results cannot be characterized as a stunning success in the case of stem cells. Stem cell research has led to great advances in our understanding of differentiation. As I wrote, the very simple observations that inhibition of Erk1/2, and activation of p38 can mimic effects of growth factors such as BMP4, FGF and VEGF acting in conjunction with clues from the matrix developing as structural cells provide a foundation for development, ranging from fetal development to wound repair, is one startling finding that holds both clinical and basic ramifications. Annals of Neurosciences was not revitalised with the

intent of meeting the format of established traditional journals. Running profiles of present investigators in fields as diverse as Physics and Philosophy while re-running portions of the works of prior pioneers does not meet the format of established journals either. But these features do provide background, reason and induce thought in a manner lost by traditional journals, who criticise stem cell transdifferentiation in 2 reports in one issue and in the next run a now widely dismissed report of transdifferentiation of the progeny of a single adult stem cell termed the MAPC (adult multipotential progenitor cell, frequency of 1/1000000 cells in marrow and 0 in blood, until that was questioned) to generate structures of all 3 germinal origins. Bone marrow biopsy puts that rather large needle through vessels, muscle, nerves, skin, and other structures as it enters the mesenchyme of the marrow stroma. A high degree of selection and selective expansion of selected cells explained the growth of some structures from the output cells in this case. The growth of neurons is still held as highly controversial.

I do hope as Dr. Anand has stressed that patient's narratives and commentaries fuel and do not hinder further discussion of communication in science; communications which recant patients' own experiences. Here there is a void; perhaps it is not appropriate to address this void in a peer-reviewed journal. As long as the rules are clear there are no rules regarding what can and cannot be published. On the other hand, there are many questions of what should and should not be run. Having a paper pass peer review is not the final answer to this very complex question, as the peer review system is becoming hopelessly tainted. Of course, errors reviewers shall make. But when reviews are pushed by profit, all bets are off. Certainly, stem cells have been oversold, but the advances stem cell research have brought have not.

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Stem Cells and Development

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