

## What is innovation?

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**H**ow do we avoid falling in the water or how do we climb out after having fallen in? Knowledge, or innovation, or both. Presumably medical journals provide knowledge, although that may be questioned in the broader context of “what is knowledge?”<sup>1</sup>

This supplement is meant to feature innovation, although, by intention, there is some “knowledge” (or perhaps, alternatively described as “previous innovation”) worth describing, lest it be forgotten. What is innovation? Is it the initial concept? Is it the proof of concept? Is it the implementation? Is it the proof that something “new” is effective? Is it always possible to discover the origins of a concept? Most often is there a single origin of a concept, or is there a development trail, or perhaps parallel developments?

The cover of this supplement was chosen for several reasons. First, the art itself. Beyond that, it highlights some interesting points. Pieter Bruegel the Elder's engraving was executed in the same year (1568) as his famous painting of the same name, “The Blind Leading the Blind,” that hangs in the Naples Museo Nazionale di Capodimonte. Which came first? Which was the innovation? Artists of the 16th and 17th centuries sometimes used etchings as studies for paintings; at times, the reverse was true. Furthermore, both were preceded by 9 years (1559) by his painting, “Flemish Proverbs,” now in the Gemälde Galerie in Berlin, in which the smallest of figures in the farthest distance appear to be one blind person leading two others. Bruegel depicted a series of proverbs, and traditionally their origins have been attributed to the New Testament. However, Sullivan<sup>2</sup> cites Erasmus,<sup>3</sup> who noted at least in the case of this proverb, that its origin can be traced, as well, to Horace, who wrote one to perhaps two centuries earlier than period of the writing of the New Testament. The issue is further entangled, in that the New Testament was written in the version of Greek that was common at that time. Thus, it is possible that there are two distinct lines of innovative heritage operating. Some of the proverbs can also be traced to Hebrew roots.

Thus, what may appear to be an innovative concept sometimes is not. The origin may be obscure and difficult to find. Only four impressions are known of the engraving on the cover (N. Orenstein, Curator Department of Drawings and Prints, The Metropolitan Museum of Art New

York, personal communication, 2012).<sup>4</sup> Descriptions of the painting make no reference to the engraving and museums rarely offer public display of their prints.

In medical writing modesty, the lack of prominence, author self-importance, or lack of appropriate citation, as occurs, at times, may leave the true innovator forgotten. Returning to art, for example, it is unclear if cubism was first developed by Braque or Picasso or whether they independently developed it nearly simultaneously or perhaps they developed it jointly, yet it is nearly universally attributed to the latter, likely owing to his greater renown.

In answering the questions posed at the outset, I believe that innovation may encompass all the possibilities of concept, proof of concept, and implementation, as each step may be innovative, most often requiring many mini-innovative components. Concepts may be attributable to a single source or, perhaps, more frequently multiple sources, as appears to be the case for Bruegel's painting and engraving. As in this case, often it is difficult to discern. His art and innovation is not lessened for having developed and implemented a concept that had originated at least 1500 years earlier, but depicted in a different and innovative manner.

In this supplement of **TRANSFUSION**, we have examples of each: concept, development, implementation, and proof. In some cases, as happens in medical science not infrequently, observation or implementation precede our understanding of the underlying basis or mechanism, as is demonstrated in the papers by the groups led by Cap<sup>5</sup> and by Pati<sup>6</sup> exploring why platelets stored at 4°C function better and for longer periods than do platelets stored at

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**ABBREVIATION:** PRT(s) = pathogen reduction technology(-ies).

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22°C (as was demonstrated—at least the function—by Valeri 40 years ago<sup>7</sup>).

Another example of a lost innovation, now reemerging, with new technologies, is that of dried plasma. Pusa-teri and colleagues<sup>8</sup> describe the current protracted, difficult (perhaps unnecessarily so) development plans in the United States. One may legitimately question why a product that was fielded, but then withdrawn owing to a problem that was solved long ago (transfusion-transmitted hepatitis), now requires an approval process that is likely to take a decade. Other innovations for blood, blood components, and associated logistics, as developed by the US military, are articulated by Gonzales and coworkers.<sup>9</sup> We owe enormous gratitude to those in uniform who made exceptional advances in this field, many of which have found their way into everyday civilian medical practice.

A concept that seems novel, but should never have been, is described by Baikumanova and colleagues:<sup>10</sup> the innate variability of blood components. Many (especially “users”) have regarded these biologics in the same manner as that for drugs: that is, they are “produced” to certain standards with minimal variability. Given the substantial differences among people, that was ever a misguided concept for these biologics, and this group of investigators, and others,<sup>11</sup> are beginning to provide illumination, thus decreasing our blindness.

Beyond all of the above, it is insufficient to innovate; one must have some evidence that the innovation is efficacious and useful. Would Szilard’s concept of a nuclear chain reaction (in September 1933, 5 years *before* the discovery of nuclear fission!)<sup>12-14</sup> have been recognized had not he with Fermi, 9 years later in December 1942 (again, with the full credit nearly always ascribed to the latter), actually produced one? (The politicized Nobel Committee awarded neither Szilard nor Fermi for these accomplishments. Fermi’s award in 1938 was for other deserving work.) Amassing data to prove a point can take years and is never complete: as medical practice changes, thus changing conditions of use, rendering some technologies to a secondary position or even obsolete.

Shander and coworkers<sup>15</sup> offer some insight into the development of and what remains to be done for patient blood management. They point out the difficulties in documenting the efficacy or safety of a new concept or technology once adopted, as its introduction can make a contemporaneous comparison impossible. In this regard, Letowska and colleagues<sup>16</sup> and Corash and Benjamin<sup>17</sup> provide some safety data for pathogen reduction, and Jimenez-Marco and coworkers<sup>18</sup> review the knotty problem of possible transfusion-transmitted *Leishmania* and why innovations now preclude full assessment. The problem is further compounded in children, by the considerable difficulties routinely encountered in attempting to

conduct randomized trials in this population. Trakhtman and coworkers<sup>19</sup> provide an alternative: a retrospective database analysis of use of pathogen reduction technology (PRT) platelets in a pediatric hematology-oncology population.

Much of the world has approved two somewhat differing PRTs (both use ultraviolet light illumination, one in combination with riboflavin and the other with amotosalen). Only recently did the US Food and Drug Administration approve the latter (December 2014). The article by Cap and colleagues<sup>20</sup> details in vitro reduction of Ebola virus in nonhuman primate serum and human whole blood by the former PRT technology. Safety has been examined in a variety of ways, but true clinical efficacy of the process (not merely cell counts or concentrations of various “things”) would be difficult to prove in most clinical circumstances, owing to the very low incidence of transfusion transmission of vectors in the developed world. A notable exception has been the recently reported successful randomized trial demonstrating reduction of transfusion-transmitted malaria in a geographic region in which malaria is endemic.<sup>21-23</sup>

Having stumbled blindly and fallen into the ditch (painting) or water (engraving) about many things, for example, the need of whole blood rather than components for trauma and hemorrhage,<sup>24,25</sup> it has been difficult to extract ourselves. It is hoped that this supplement will assist for the issues addressed.

#### CONFLICT OF INTEREST

The author consults for TerumoBCT, the sponsor of this Supplement. The author did not receive any compensation for work associated with this editorial or the Supplement.

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