Tom Layloff

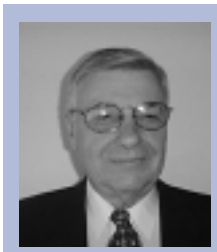
Will Others Be Able to Stand on Our Shoulders?

*"If I have seen further, it is by standing on the shoulders of giants."**

If we reflect on the great advances in therapeutic products that enrich our lives, we must give credit to those members of humanity who, initially by happenstance and later by design, brought us to our current therapeutic pinnacle or inflection point. Who was the person with a headache who discovered that chewing on willow bark relieved the symptoms? Who was the "traditional healer" who interviewed that person and incorporated willow bark into his/her therapeutic medicine bag? And who was the person who found that the active therapeutic compound was salicin? That salicin was later found to be a salicylate derivative led to the therapeutic salicylate trail that eventually led to the synthesis of aspirin. This move from an extractive therapeutic source to chemical manufacture was a remarkable transition that eventually created a multitude of employment opportunities for scientists from many disciplines, which continues to this day. This transition was a major industrial innovation which, in itself, was a part of "this irresistible revolution that for so many centuries has marched over all obstacles, and that one sees still advancing today…"[1] (emphasis added by author).

Who was the person who first chewed *Rauwolfia serpentina,* discovered its therapeutic activity, and reported it to the traditional healer to lead us eventually to reserpine? And what of the poor souls who gnawed on *Digitalis purpurea* to discover the cardiotonic effect of the glycosides digitoxin and digoxin, which ultimately led to their isolation and characterization (see www.britannica.com/eb/article?eu=30928>)? The discovery trail from the new-mown hay blood anticoagulant isolate coumadin is well-documented (Coumadin was trade named by the Wisconsin Alumni Research Foundation [WARF] as Warfarin). An undesirable property in animal farming, hemorrhaging, led to a desirable animal extermination property, rat poison, and finally to a desirable human health intervention, blood thinning. And who discovered the therapeutic properties of Cascara Sagrada, the laxative (Cascara Sagrada, Spanish for sacred bark is the dried bark of the buckthorn *Rhamnus purshiana* [order Rhamnales], which is used in medicine as a laxative), and ipecac, the emetic that has saved thousands of children from their misdirected culinary experimentation (ipecac is an emetic and expectorant drug that contains emetine and is prepared from ipecac, especially as a syrup for use in treating accidental poisoning)? These will forever remain myster-

*Sir Isaac Newton, quoted at www.quoteworld.org/search.php?thetext=isaac+newton&x=18&y=9.



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ies in the history of mankind, but are some of the shoulders upon which we stand to see further.

This trail of therapeutics eventually expanded to include animal-derived products such as insulin, thyroid extracts, and pituitary extracts, etc., while the continuing deluge of plant material extracts and derivatives investigations brought products like taxol to our therapeutic armamentarium. This trail led first through chemical purification of plant and animal extracts to the identification of well-defined chemical entities. Those chemistry successes eventually resulted in the search for therapeutics to chemists' storerooms, where classes of chemical agents not based on a natural source product were discovered, e.g., sulfa drugs and betablockers. These successes culminated in the establishment of our great pharmaceutical industries.

In the pursuit of new therapeutic entities, chemists have expanded their storerooms by introducing automation and high-throughput syntheses and screening. These high-technology introductions have provided an astounding array of potential therapeutic interventions. In addition to these synthetic innovations with which to identify candidates, there continues a vast parallel effort to scour the lands and oceans of the world to identify additional natural source therapeutics. We became so enamored with our technological achievements that we ignored the centuries of hit-or-miss human experimentation that gave rise to the therapeutic repertoires of traditional healers as possible sources of new products. However, in our current frenzy to identify new therapeutic leads, those traditional healers have been resurrected as participants in the process to fill the screening laboratory pipelines.

All of this effort has brought forth an astounding array of potential therapeutic interventions. These potential interventions then undergo an equally astounding product development attrition rate: Only 5 in 5000 or 0.1% of the potential therapeutic entities identified advance through preclinical testing to U.S. FDA filings as investigational new drugs (INDs).[2] This preclinical development stage is conducted over a ca. 3.5–year period and involves laboratory and animal studies conducted to assess safety and biological activity. As noted, 99.9% of the preclinical candidates fail some aspect of the assessments and are dropped from further development. From these preclinical tests, five substances advance for submission to the FDA for testing as INDs (the IND phases and steps are presented in detail at www.oprs.ucla.edu/human/hspcmanual/9D.htm).

Phase 1 IND testing is conducted over a one-year period on approx. 20–80 healthy volunteers to further explore the product safety and to fine-tune the dosage levels. The Phase 2 IND testing level is conducted over a ca. two-year period with 100–300 patient volunteers to evaluate effectiveness and possible side effects. Following this testing, the products enter Phase 3 IND testing over a ca. three-year period, with 1000–3000 patient volunteers. Phase 3 helps to verify effectiveness and further monitors adverse reactions from long-term use. If all of this testing is satisfactory a new drug application (NDA) is filed with the FDA for approval. Of five NDAs submitted, only one is ultimately approved for marketing and Phase 4 follow-up studies. The overall attrition is from 5000 preclinical candidates to one approved product; only 0.02% of the starting pipeline makes it through to an approved product.

In 2001, pharmaceutical and biotechnology companies added 32 new treatments to the nation's medicine chest—24 drugs and 8 biologics—and invested an estimated $30.3 billion in R&D (see www.phrma.org/press/newsreleases//2002-01-25.329.phtml). The average cost of bringing a prescription drug to market in 2000 was estimated to be ca. $800 million, according to a study by The Tufts Center for the Study of Drug Development (see http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6). This amount per drug in 2000 for the 32 entities approved in 2001 is consistent with the 2001 estimated $30.3 billion R&D investment. This level of drug development investment is on the order of the recently approved $27 billion annual budget of the entire U.S. National Institutes of Health (NIH) (as reported in *Science*, www.sciencemag.org/cgi/content/full/297/5581/493a).

In addition to this vast therapeutic development investment targeted for FDA approval for product marketing, there are a number of other government programs that require the submission of biological safety test data for product approval, e.g., FDA for food additive approval; U.S. EPA for products and degradants; NIOSH for material safety data sheets (MSDS) chemical exposures, etc. The bottom line is that we as a scientific industrial society generate an extraordinary amount of safety and toxicology data for the development of therapeutic agents and to protect our health from various and sundry chemical entities, both natural and synthetic.

What becomes of the data obtained through this vast societal undertaking? For each approved new drug through the IND process there are 3220–9640 person-years of controlled exposure to a chemical entity. For the four substances that entered the IND testing but were not approved, there are an additional 12,880–38,560 person-years of controlled exposure. This amount of controlled exposure is expended annually for drug development only, and does not include studies for other safety and toxicology assessments. Of course, there is also extensive laboratory and animal testing performed on the ca. 4995 chemical entities that did not pass muster to be advanced into the preclinical development. As noted previously, in addition to this drug development enterprise, there is extensive animal and human testing conducted for other agencies.

What becomes of this magnificent mountain of data? Is it warehoused in locations reminiscent of the last scene of the film, *Raiders of the Lost Ark*? Is it buried and lost to the enrichment of our science and knowledge? It is archived in knowledge dead-ends and lost to exploitation by the new information technologies such as Web-browsing with learning machines and artificial intelligence. Over the years, retrospective structure–activity relationships (SARs) have been developed to help guide the production of new therapeutics. The quality of these SAR investigations can be no better than the quality of the data being mined. Further, the SAR development model is a limited concept that cannot include the full richness of all of the safety, efficacy, and toxicology data accumulated through these various programs.

What should be done?

1. U.S. federal legislation should be passed that requires the public release of all toxicological and safety data

submitted to the government three years after the date of receipt of the submission.

2. A contract should be issued to a large, competent scientific abstracting and database-generating organization to first develop standard descriptors and data formats for toxicology and safety data, and second to begin establishing the database starting with the most recent public released data, i.e., after the three-year submission period, and then move retrospectively through the mountains of data to place them in the standard descriptor and data formats. (The American Chemical Society Chemical Abstract Service is such an organization; see www.cas.org)
3. The ordered data should then be made publicly available so that academicians, industries, interested individuals, etc., could contemplate, machine search, and glean new correlations and knowledge with artificial intelligence learning machines.

Of course, there will be flaws in some of the data in addition to errors, omissions, and probably some instances of fraud. However, they will be few, and if we focus on these, we will miss the magnificence of this great resource. Making these databases available to the public will elicit an array of headline-seeking muckrakers and bottom-feeders to attack various aspects of this scientific enterprise. However, that risk would be more than offset by the opportunities presented to bright and aggressive scientists to use those data to make striking advancements in the design of new therapeutic interventions as well as new insights into possible hazards to substance exposure.

There are property rights issues concerning the release of these proprietary submissions. However, there are also human rights involved in that it is highly likely that the databases will reduce the amount of human testing required for the IND phase drug investigations and other chemical testing. There are also animal rights involved in that similar reductions in the preclinical search for new target products would occur because the improved drug targets would have less attrition. There would also be a significant reduction in animal testing to support safety evaluations for MSDSs, etc.

Lastly, of course, there are humanity's rights. We stand on the shoulders of giants who have come before us. The question is: Can we bring forth the shoulders of the pharmaceutical industrial revolution and the related chemical processing revolution for the information age to stand on so that we can see further? It is time to consider the next generation of scientists. That is our ongoing debt to the irresistible revolution that has brought us here.

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