Watch Out for the Little Guy

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It is often difficult to explain why scientific advancement is an inherently inefficient process. In my previous life as an engineer, it was straightforward to establish a goal, and apply known laws of physics/chemistry to achieve that goal. Individuals with experience in the R&D sector often suggest that a similar approach should be used in biomedical science. But, it is often surprising to learn the sources of important scientific ideas. An excellent example is the medicine exenatide, which is marketed as Byetta (by way of disclosure I am a consultant and grantee of the Amylin Corporation). This medicine has proven to be a boon to patients with type 2 diabetes because of its ability to improve glucose tolerance and reduce body weight in many individuals. The agent is based upon basic research into the hormone glucagon-like peptide-1 (GLP-1), secreted by the L-cells of the gastrointestinal tract. Several investigators, notably including Jens Holst of Denmark (1), laid out the fundamental effects of this protein in man, and his pioneering studies have been followed by many others. But GLP-1 has a rapid disappearance half-life from plasma, making it difficult to exploit its positive effects in human patients. Exenatide emerged as an excellent alternative. But the discovery of exenatide and its potential as a therapeutic agent could hardly have been predicted by any “research guru.” Dr John Eng isolated exenatide from the saliva of the Gila monster (2). The protein is somewhat homologous with GLP-1, but it has a considerably longer half-life. Which R&D “expert” would have suggested studying the Gila monster to find an alternative to GLP-1? The rest, as they say, is history. Another example: Turing’s paper “On Computable Numbers, with an Application to the Entscheidungsproblem” (3), the theoretical basis for the digital computer, was published by Turing in 1936 but remained essentially uncited for many years. Our own work on the minimal model (forgive me for a personal reference) was likewise essentially uncited for the first 5–6 years after it was written (4), but the work has been cited about 100 times per year for the last 25 years. Many scientists have similar tales.

Trends today, unfortunately, point away from support for the iconoclastic, individualistic scientist. Increasing funds point toward “directed” programs, which are often expensive, potentially useful but of limited novelty or innovation. Promising junior scientists are increasingly disheartened by low probabilities of being supported, and an increasing cadre of productive, highly regarded senior scientists have “bailed out” of basic and clinical research. This latter problem is particularly acute in obesity and diabetes research. It is time to stem the tide! I suggest (I am not the first) that the funding agencies protect, at all costs, the “pay line” of original research (the R01 mechanism). Large programs, “big science,” should only be supported if the funds are available after the R01 pay line (23%) is covered. This approach would guarantee that promising junior scientists, midlevel scientists doing outstanding work, and proven, productive senior scientists could continue to contribute, without having to spend half their time raising money, or leaving research for lucrative careers in the private sector, possibly out of the scientific mainstream. It is high time for the advocates of research advancement to voice the point of view discussed herein, to guarantee a vibrant future for basic and clinical biomedical research in the United States and elsewhere. That we have reached a crisis which has deeply affected the scientific community is little understood by our elected representatives, or by the voting public. It is time for leaders to step out and speak up to re-engineer (there is that word again) our scientific community. We know that being a scientist is one of the most prestigious occupations (5); it is now high time to re-stabilize support so that we can recruit the most talented and provide for them a “road map” for their futures and those of their students, trainees, colleagues, and families.

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