MAKING PROGRESS: DOES CLINICAL RESEARCH LEAD TO BREAKTHROUGHS IN BASIC BIOMEDICAL SCIENCES?

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The need for basic science research to generate advances in clinical understanding of disease biology is an axiom of biomedical research and has no credible opposition (see [1]). However, a corollary is often drawn, that this is a one-way process; in other words, basic biology advances do not follow from applied or targeted (clinical) research. This is entirely wrong. Ever since the beginnings of scientific medicine, clinical observations have repeatedly generated breakthroughs in biology that could not, at the time, have been otherwise achieved. This assertion has been made before [2, 3], but it bears repeating now, particularly in relation to clinical observations on disease or its treatment, followed by research aimed at identifying a biological aspect or mechanism of these observations (called disease-oriented research [DOR] by Goldstein and Brown [4]).

There are many historical examples that exemplify this point, and I have chosen two instances to present here: the discovery in the 1940s that DNA is the substance that carries genetic information, and the discovery in the 1990s of unstable DNA sequences as a new mechanism of mutation. These are basic science breakthroughs, discoveries of new biological mechanisms of fundamental importance beyond the diseases on which the researchers were working.

For a reader not immersed in today's biomedical research community, it might seem obvious that these are indeed basic science breakthroughs, but it would also appear that they resulted from basic research. The popular understanding is that basic science is what occurs in the laboratory and clinical research is research on patients in the clinic or hospital. Within

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the research community, however, the prevailing outlook conceives of two types of research, basic research and applied (including clinical) research. Basic research, in this view, is research based on a hypothesis about how biology works (e.g., that a certain enzyme exists), whereas clinical research is applied research, which determines if known biological mechanisms apply to a disease or treatment (e.g., testing whether this now-discovered enzyme is altered in a particular disease).

It is also generally understood that the borderline between the two kinds of work is not always distinct, and in recent years the concept of "translational research" has come into use. Now, translation from one spoken language to another can flow in either direction, but as currently used in biomedical research, translational research refers to a one-way process in which the findings of basic research are applied to clinical problems. This derives from the sense in which translation is used in molecular biology to refer to the decoding of information contained in a nucleic acid sequence to determine the amino acid sequence of a protein. Although the term is useful to describe research that joins basic and clinical work, its use reveals the prevailing directional bias that the most basic (and most important) discoveries are made in the basic laboratory and applied to the clinic.

This bias is a costly one. It enshrines an antagonistic "two cultures" mentality in the vast segment of society related to biomedicine, and it inhibits intellectual voyages of discovery that do not go in the prescribed direction, thus inhibiting rather than stimulating scientific progress. To show that these consequences are plausible, I will offer a brief description of two historical breakthroughs that occurred, about 50 years apart, in the course of applied laboratory research on disease characteristics. In each case, the discovery would not have followed from the basic science of its day, but did follow from the intellectual temerity of the researcher wrestling with a clinical question.

The Discovery that DNA Is the Substance that Contains Genetic Information

Oswald Avery, a physician researcher, at the Rockefeller Institute, labored with his colleagues for many years to discover the basis of the extraordinary infectious virulence of pneumococci. It had been found that pneumococci varied greatly in their virulence, and understanding the basis of this variation appeared important for diagnosis and for development of antisera as therapy. The phenomenon of transformation of live pneumococci from non-virulent to virulent by addition of dead, virulent pneumococci had been reported in 1928 (the account here is based on [5]). It had also been demonstrated that this occurred chemically, by addition of an extract of killed virulent pneumococci, and that these now-virulent pneumococci would breed true (as virulent organisms) indefinitely. By various

experiments Avery and colleagues proved that the "transforming principle" was not a protein (at the time, genes were thought to be proteins), but was DNA. In their landmark 1944 paper they did not go so far as to state explicitly that DNA was the substance of the gene, although Avery did state this in private correspondence and discussions, and his paper rigorously proves this very point [6].

This finding gave rise to enormous criticism and disbelief among the leading geneticists of his time, particularly at their own Institute, and the recognition of the importance of this finding was belated. A Nobel Prize was not awarded. One reason for the resistance is that this was a true Kuhnian paradigm shift [7]: DNA was thought to be a "dumb substance" at the time, consisting of four nucelotides in unvarying proportions. Another reason is indicated by the venue in which the work was published—the *Journal of Experimental Medicine.* Avery was an outsider, a physician-researcher concerned with elucidating the basis of disease virulence, rather than one of the "phage group" of physicists/geneticists, led primarily by Max Delbrück, who were the leading workers at the time on the general problem of the physical basis of inheritance. In his interview in Judson's book, Delbrück describes struggling with this finding but remaining not quite convinced until the physical basis of encoding by DNA was proposed by Watson and Crick in 1952 [5].

Unstable DNA: Trinucleotide Repeat Expansion Is a New Mechanism of Mutation and of Human Disease

This very striking advance in understanding the nature of mutation and of gene stability followed from applied genetic research in inherited diseases in the past few years. The laboratory methods that led to the initial discoveries were "off the shelf," and the hypothesis being tested was not a hypothesis on a new biological mechanism that might exist, but the by now almost prosaic search for the mutation responsible for an inherited disease. This is the kind of laboratory research called "applied" and "clinical" in the biomedical sciences. Research on a human disease is no longer considered "basic" if it does not attempt to develop a general technical innovation or to test a hypothesis about a biological mechanism.

Several laboratories came to the idea of trinucleotide repeat expansion in the same year (1991) [8–12]. Kremer, et al., were applying standard cloning and sequencing methods to a small chromosomal region previously identified as having the gene for Fragile-X mental retardation [9]. It was also known that the disease gene was unstable, in that it was greatly enlarged in ill offspring but not in the well parents. They showed that the unstable DNA was in the same location as the CCG trinucleotide repeat in the gene and speculated that expansion of the repeat was the mutation that caused the disease. The speculation was quickly borne out for Fragile-X and for

a series of other neurological diseases, including Huntington's disease, where the disease mutation had resisted discovery for a decade, partly because the type of mutation (expanding trinucleotide repeats) was completely unsuspected [13]. This mechanism constitutes a new form of genetic mutation. A previously unexplainable pattern of inheritance of certain single-gene diseases, anticipation (more frequent and worse disease in successive generations), was also found to follow from the changes in the size of the expansion. The basic mechanism for the instability remains undiscovered, and it is being explored by a great number of basic science laboratories.

How Can We Now Encourage Such Breakthroughs?

There are several lessons to be learned from these scientific triumphs, and from numerous other discoveries that followed from clinical investigation. The process of discovery, particularly discovery of radically new and seminal findings, is almost by definition full of unanticipated developments. Why are careful clinical observation and applied research into clinical disorders such a rich source of these developments? Perhaps one answer is that disease very often reveals the "ingenuity" of nature, and the human race includes several billion individuals who are, in effect, continually examining themselves for new examples of this ingenuity to bring to the attention of biomedical science.

Another factor is that the biomedical scientist who successfully takes on these problems has most often followed Louis Pasteur's famous dictum, "Fortune favors the prepared mind." In our examples, their minds were prepared by the preceding clinical phenomenologic and laboratory investigations. In the Fragile-X case, on the clinical side this included the clinical description of a pattern consistent with X-chromosome inheritance in some families with mental retardation in the 1940s, the discovery of a cytogenetic abnormality (fragility) of the X-chromosome in some of these patients in 1967, and the careful clinical investigation of multiple members of pedigrees with this disorder, including well persons who transmitted illness, in the following decades.

It follows that neither the policy makers making research funding allocations, nor the biomedical scientist planning his or her own investigations, should draw a line in a doctrinaire manner between applied (clinical) and basic work. The line is a fuzzy one, and each will complement the other in essentially unpredictable ways. Nevertheless, within the scientific community, and in public policy debate, a line is drawn which sometimes seems to be a border between two nations not entirely at peace with each other. There continues to be a widely expressed concern among the most distinguished biomedical scientists that it is "basic research" which is endangered, a fear substantiated by the criticism of members of Congress who

"in asking federally supported academic investigators [to] become responsible for practical applications, . . . ignore the demonstrated ability of the biotechnology and pharmaceutical industries to develop the fruits of basic science" [1]. One would hope that federal support and these industries would simultaneously pursue both basic science and its [clinical] fruits, since in this instance as in the case of a fruit orchard it is short-sighted to create a distinction between the well-being of the fruit and the well-being of the trees.

In the U.S., federal policy on the relative support of clinical versus basic biomedical research is largely played out at the National Institutes of Health (NIH). This is the agency with the largest investment in all types of biomedical research, and it is the one where the issue has repeatedly been raised recently of how much of each is really needed. All parties to the various policy arguments would agree that both are needed, but at this point the argument is clearly still prevailing that there is too much clinical and not enough basic science research supported by NIH. Particularly in the NIH intramural programs, where the zero-sum aspect of funding has led to an acute competition for resources between clinical and basic investigators, over the past generation there has been a pronounced tilt away from clinical investigation. The number of research beds at the NIH Clinical Center, for example, will be reduced by about half with the construction of a new Clinical Center over the next decade.

A paper such as this one cannot begin to assess whether the current balance is adequate or not for scientific progress, but it can present the argument that a balance is needed, not just to satisfy the different constituencies but to enable basic biomedical science to progress. It is historically true, although counterintuitive, that clinical research has repeatedly generated breakthroughs in biologic mechanisms, particularly mechanisms of disease. From this viewpoint, a funding policy is needed which supports the last steps (that is, research which does produce a breakthrough), as well as the earlier steps, whether they are basic or applied. The earlier steps include basic as well as clinical investigation, that is, incremental science research. A biomedical research support policy which devalues one type of research as compared with the other undermines intellectual flexibility and preparedness for leaps of inspiration which produce the breakthroughs we desire. Within the biomedical scientific community, the challenges of clinical investigation must be recognized. Support decisions by scientific review committees should be based on ability to recognize and answer these challenges, and not on how much the work is similar to current basic science research or—even worse—on whether the investigator is a basic scientist or not. It is unwise to generate strict separations between clinical and basic research, as a recent NIH Blue Ribbon panel did in offering as a policy: "the placement of basic scientists in clinical laboratories should be rare" [14].

Resistance to Breakthrough Research

Historically, major scientific breakthroughs often have come by breaking widely accepted scientific paradigms and have been resisted initially by investigators working incrementally within established paradigms, as elucidated by Thomas Kuhn several decades ago [7]. I have focused on genetic examples in this paper because of my familiarity with them, but historically genetics is only one of many fields of biomedical science which have experienced clinically driven paradigm shifts. Yet another genetic paradigm shift, and one which is still taking hold, has resulted from the development of the human gene map in the past decade. For inherited diseases it has become possible to locate the gene(s) responsible by genetic linkage mapping, without any clue as to the nature of these genes, and to discover subsequently the biology of the gene and the role of its product in pathophysiology. When this method was first developed, it was aptly called "reverse genetics," since it was a profound reversal of the previous paradigm, where first an abnormal gene product was identified for a disease and then the gene was found. The term also reflected the feeling of many traditional investigators that this was research turned upside down and made mindless, a reaction which is not uncommon when a shift occurs. Not surprisingly, we now use the more neutral description "positional cloning."

If we define one kind of breakthrough in biomedical science as the discovery of a previously unknown disease mechanism, the most striking breakthroughs of reverse genetics can be expected where the initial knowledge of biological mechanism is weakest. I once heard James Watson remark in conversation that each of the discoveries of cancer-causing mechanisms by reverse genetics has been a complete surprise, although I'm certain he was mindful of the advances in cell biology which made the surprises comprehensible. It is no longer high-risk or paradigm-breaking research to find cancer genes by reverse genetics in pedigree studies, but for a considerable time it was. Cancer is a complex and common disease, with numerous independent forms with separate known inherited mutations, and until recently many geneticists felt that this precluded use of reverse genetic methods.

Behavior, including inherited mental illness, may present an opportunity for major discoveries from reverse genetics, similar to the opportunity in cancer. The neurosciences as a whole are not sufficiently advanced to have testable biological models of advanced behavior, as there are few applicable cellular or animal models and the inheritance pattern is quite complex. The genes for Huntington's disease and Fragile-X mental retardation, whose discovery was described above, have become the subject of much basic investigation to discover what their normal function is, and through that to discover something about psychosis (which is often present at the outset of Huntington's disease) and intelligence. As exciting and challeng-

ing as this extension of recent findings would be, the application of reverse genetics (positional cloning) to human behavior appears to offer a greater opportunity at this time, because there are undoubtedly numerous unsuspected genes waiting to be discovered.

What are the prospective criteria for breakthrough research? One cannot set predictive criteria for an event which is most often surprising. But it is worth looking at major advances and having mechanisms built into funding and policy decisions for supporting this type of work. From the peer review and programmatic viewpoint, such work may look as if it doesn't merit funding or publication, yet Nobel prizes have been awarded for work which had great difficulty getting past editorial review by respected journals, as in the well-known example of Berson and Yalow's development of radioimmunoassay. The questions may seem audacious, even foolish, the risk may seem very high, the underlying paradigm not quite acceptable. Perhaps even worse, the work may seem both foolish and pedestrian; some early disease mapping studies seemed that way until they were successful. If one criterion, then, is that such work does not do well in large committees, it may be necessary to set up committees of one or two scientists with outstanding records of recognizing and stimulating paradigm-breaking innovativeness, and to give them discretion to award a certain (small) proportion of total support to otherwise unfunded ideas.

But the most general solution is for all persons involved in performing and supporting biomedical research to recognize that ground-breaking innovations can come from clinical research, as well as from basic science. Where the interests of clinical and basic investigators overlap, a new sense is needed of partnership, mutual respect, and understanding of the standards for intellectual rigor and innovation in the pertinent clinical and basic fields. Particular support is needed for scientists, whatever their original training, who are bridging both types of investigation; when successful, they are very successful indeed.

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