Perspectives

Presidential Address 2002—Genes, Brains, and Behavior: The Road Ahead

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We live in extraordinary times. Advances in the life sciences have the potential to revolutionize health care as well as the actual quality of life that many of us experience. Indeed, the explosive growth in our knowledge of human development and aging on a wide variety of fronts is already having an impact in the wealthy countries of the world. Life spans are increasing and treatment options for a wide variety of disorders and disabilities multiplying. Will this knowledge ultimately benefit individuals with intellectual and developmental disabilities? Can it really change the quality of life they experience? What really lies ahead?

My purpose here is to speculate on the future of biobehavioral science and the opportunities and pitfalls it holds for individuals with intellectual and developmental disabilities. I first discuss, on a nontechnical level, examples of recent advances in genetics and neuroscience as a means of highlighting some of the potential these areas of science hold. In the course of these discussions, I highlight some of the opportunities that advances in these areas hold for understanding the effects of the environment on development, particularly for enhancing the effectiveness of behavioral interventions. I then discuss some of the challenges that must be met if the potential of an emerging biobehavioral science of human development and functioning is to be fully realized in the years ahead.

Genes

Biomedical research is increasingly dominated by a genocentric point of view—and with good reason. Our knowledge of the varied roles that genes play in human development and functioning at both the biological and behavioral levels is expanding at an explosive rate that shows no signs of abating. The deciphering of the human genome, while an extraordinary scientific and technical accomplishment, is just the starting point. We now know how all the roughly one billion "words" (i.e., base protein combinations) in the book of life (i.e., the full human genome consisting of approximately 30,000 genes spread across 23 chromosomes) are spelled. We have a very long way to go, however, in our understanding of what these *words* mean (i.e., the function of each one).

Translating the "book of life" into meaningful knowledge that can be used in solving the complex riddles of human development will require extraordinary advances in the years ahead. Scientists are attacking these riddles from a variety of perspectives, using an array of sophisticated tools. As a result, new treatments are already on the horizon and in experimental use in animal models and, increasingly, with humans. Consider these examples of progress.

- Sometime in the near future, somatic gene therapy in utero or soon after birth may offer an effective means of correcting some birth defects. Interventions of this sort are in development throughout the world (Ye, Mitchell, Newman, & Batshaw, 2001).
- Therapeutic benefits of gene therapy with human beings have been recently demonstrated with hemophilia B and X-linked immunodeficiency (Seppa, 2000).
- Inheritable genetic modifications (IGM) offer the real possibility of preventing the inheritance of genetically based disorders, such as fragile X syndrome (Verma & Somia, 1997).
- Several potentially effective gene therapy techniques are in the initial phases of development. These include *spellchecker* techniques, in which DNA is probed to determine whether important genes contain serious "misspellings," which can then be corrected. Other applications include the development of artificial chromosomes and, most promising, the development of a variety of trans-

genic techniques in which new genetic information is inserted into chromosomes to cause a "bad gene" to turn off and/or a "good gene" to turn on (Stock, 2002).

- Several genetic disorders have already been successfully prevented in mouse models using transgenic techniques. These disorders include Lesch-Nyhan disorder, dwarfism, and sickle cell disease. Of particular note is the successful "cure" of fragile X syndrome in a fruit fly model using transgenic techniques (Pawliuk et al., 2001; Sohn, 2001).

Despite these and other reported advances, many gene therapy approaches may never prove sufficiently safe to use with human beings (Verma & Somia, 1997; Ye et al., 2001). Furthermore, curing fragile X in a fruit fly may not translate into a cure for fragile X in humans. Still, gene therapy is a rapidly developing area of medicine with extraordinary potential. Nevertheless, the greatest impact of the genomic sciences in the years ahead is likely to be through the development of increasingly individualized pharmacological treatments for a wide range of disorders and their symptoms (Evans & Relling, 1999). More effective drugs designed to fit individual genetic make-up promise to lessen side effects as well, although the financial costs of developing, testing, and marketing such drugs represents a major challenge (Singer & Daar, 2001).

Another near term impact of the genetics revolution is our already enhanced ability to scan an individual's DNA at birth and identify a wide variety of real (e.g., presence of fragile X syndrome) or potential (a propensity to certain types of cancer) problems. The pressure to radically expand genetic screening at birth will surely grow exponentially in the years ahead, even while effective treatments or cures for many disorders will still be more dream than reality (Fukuyama, 2002; Marshell, 2001).

With all the potential inherent in the genetics revolution, it is easy to get caught up in the hype and lose sight of some fundamental caveats. It has become evident that most complex human disorders (e.g., cancer, heart disease, diabetes, schizophrenia, autism) are context-dependent entities to which our genes make a necessary, but only partial contribution (Rees, 2002; Rutter, 2002). Even single gene disorders (e.g., fragile X syndrome) are proving to be extraordinarily complex (Brodsky & Lombroro, 1998). There is plenty of evidence that highly heritable traits are often highly malleable and subject to a range of environmental influences as well (Reiss & Neiderhiser, 2002; Rutter, 2002). Traits are best described as "propensities" or "probabilities." Your genes do not determine how you behave and develop so much as they interact with the environment in ways that over relatively long periods of time influence development. Furthermore, human beings are extraordinarily adaptive creatures, with all sorts of cultural tools for modifying and managing so-called inherited traits. Even those inherited traits, which are thought to be among the most "genetically influenced," can be heavily influenced by the environment. Height is a perfect example of this. It is among the human traits that are most genetically influenced; yet the environment in the form of diet can have a huge influence on it as well. Average height in many countries has increased enormously over the course of the 20th century, almost certainly due to improved nutrition (Kuhl, Power, & Rogers, 1991).

The fact is that many genetic vulnerabilities and strengths may only be manifested in the presence of an "environmental trigger." Known environmental triggers for various problems include poor diet, chronic sleep disorders, and harsh parenting, etc. (Reiss & Neiderhiser, 2000; Rutter, 2002). On the positive side, stable, long-term, highly responsive parenting may well set the parameters for enhanced emotional, cognitive, and language development (e.g., Landry, Smith, Swank, Assel, & Vellet, 2001). In fact, cultural "practices" remain an extraordinarily powerful force in shaping development (Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000). To get a sense of this power, imagine that you could exchange a newborn baby from 20 thousand years ago with a baby born yesterday. Both children would most likely grow up to be typical members of their society, virtually indistinguishable from those born naturally into it. On the other hand, if you switched a stone-age adult with a 21st century adult, each would be in BIG TROUBLE because, although their biological make-up would be very similar, each would be a product of very different and very powerful cultural forces (Barash, 2001).

As genomic science and technology moves forward, we will increasingly be able to determine the effects of behavioral interventions on gene functioning and expression (Reiss & Neiderhiser, 2000). With a technological innovation termed a *gene chip*, scientists can place a piece of DNA on a chip that "reads" it and determines which genes on this piece of DNA are presently "on" (expressing protein) and which are “off.” Using this technology, one can determine whether a specific behavioral intervention turns certain genes on or off. At present such studies are limited primarily to animal models; but there is no theoretical or technological reason that this same technology cannot be used to study impact of behavioral interventions with human beings. We have known for some time that behavioral interventions can modify the effects of so-called “genetic disorders.” As our knowledge grows of the precise manner in which behavior impacts biological functioning, the effectiveness of our behavioral interventions should increase as well.

With the exception of a relatively small number of disorders (e.g., Huntington disease, Angelman syndrome), genes are not destiny. Instead, they work together with the environment in complex algorithms to chart the course for development. Have we entered into the “golden age” of genomic sciences? Perhaps—and, paradoxically, this may lead to a “golden age” for the behavioral sciences as well.

Brains

The human brain weighs around 3 pounds on average (Einstein’s only weighed 2.5 pounds). Contained within this small, gray, sponge-like mass are millions of neurons (brain cells) that communicate with each other through billions and billions of synaptic connections. Until we meet up with a more advanced being from another planet, the human brain holds the distinction of being the most complex known object in the universe.

If there is one topic that has received more hype than genetics, it is the purported “breakthroughs” of neuroscience—the interdisciplinary study of neural development and functioning. This hype has grown out of the discovery that a great deal of human neural development occurs after birth, particularly during the first 3 to 4 years of a child’s life, and appears to be driven in part by environmental input (National Research Council and Institute of Medicine, 2000). This fact has been interpreted by many well-meaning politicians and advocates as reflecting a “critical” period in neural development—a window during which the brain’s development may be so heavily influenced by the environment that the parameters of future potential are set (Bruer, 1999). The argument goes that if such period is “wasted,” that some degree of potential may never be recovered. This view has been reinforced by reports that a substantial proportion of children with autism who receive highly intensive early intervention end up with only minimal impairment, whereas children who receive an insufficient dose of “intensive early intervention” inevitably languish (National Research Council, 2001).

The notion that the first few years of life are a “critical period” for neural development continues to have currency. However, what neuroscience research really supports is a different matter, but one that should be far more comforting. Although early development is certainly important, the brain remains a highly “plastic” and remarkably malleable organ throughout life (Bailey, Bruer, Symons, & Lichtman, 2001). Yes, it is amazing how children can learn their native language by age 3; but if you spent 14 hours a day, 7 days a week, 365 days a year for 3 years focusing most of your attention on learning Russian, while interacting with and surrounded only by Russian speakers (similar to what infants and toddlers do in learning their first language), chances are you would become an “amazingly fluent” Russian speaker. The point is, *plasticity,* the ability of the brain to “learn,” remains a central characteristic throughout life (Bruer & Greenough, 2001). Critical periods, at least in the biological sense, are relatively rare in human beings and tend to be relatively lengthy (Bailey et al., 2001). For example, a “critical” period does appear to exist for acquiring syntax, the underlying rules of constructing grammar. However, it appears to extend up to puberty (Bortfeld & Whitehurst, 2001).

What matters most in terms of optimal neural development is early experience *and* whatever comes next. Exposure to an optimal environment early in life does not inoculate a child against the cumulative effects of ineffective elementary and secondary schools (National Research Council, 2000). However, exposure to such an optimal environment early on combined with continuing exposure to a stimulating, challenging, responsive environment later on obviously enhances the odds of optimal development. Still, nothing is guaranteed in life. The real potential of the knowledge generated by the life sciences in the years ahead will be to enhance the possibilities of optimal outcomes for individuals with intellectual and developmental disabilities.

Beyond the hype, neuroscience is rapidly advancing. Leading these advances is the development of increasingly sophisticated imaging tools for observing the brain "in action" (Lyon & Rumsey, 1996). These imaging tools are enabling neuroscientists to visualize brain sections at a resolution previously thought impossible. Perhaps, however, the greatest potential of the neurosciences resides in its integration with our rapidly expanding knowledge of genomics. It is estimated that fully one third of human genes are devoted to neural development and functioning. Neuroscientists are increasingly focusing on how genes express themselves in terms of brain function. Among the exciting spin offs of this integration should be increasingly effective hybrid intervention approaches. In fact, some of these already exist, including early cochlear implants for deafness combined with intensive early communication intervention (McKinley & Warren, 2000) and new pharmacological treatments combined with functional communication training (Schroeder, Oster-Granite, & Thompson, 2002). Others, such as brain implants plus intensive physical therapy for motor disorders, are well along in terms of experimental applications with human beings (Hockenberry, 2001; Taylor, Tillery, & Schwartz, 2002)—and these developments are just the beginning.

Potholes and Passing Lanes on the Road Ahead

It is common knowledge among life scientists that the easy problems have all been solved. The day of the lone wolf scientist isolating herself in the lab and chipping away at some basic question from the perspective of her relatively narrow discipline is all but over. Although built solidly on the backs of thousands of lone wolf types who toiled away for decades on "basic research," further progress in solving the major problems of human development and functioning will require an unprecedented degree of cross-disciplinary collaboration. This fact is made all the more daunting by the realization that however noble such collaborations may appear to outsiders, to those trying to "collaborate," it often feels like an unnatural act between two or more nonconsenting adults. Will future progress be held hostage to ancient human emotions, such as jealousy, vanity, and a caveman-like protection of "turf"? In the end, those potholes will likely be circumvented by a more powerful human desire to cooperate to ensure mutual survival and success. Still, the road ahead will be rough.

Beyond the challenge of collaboration lies a seemingly paradoxical challenge just beginning to confront life scientists. It is evident that biological organisms are inherently tuned to their environment. Genetic factors alone typically account for only a fraction of variance in human behavior. To account for the remaining variance, that is, to fully understand development and behavior, scientists must increasingly move toward analyses of functional interactions between biology, environment, and behavior (Reiss & Neiderhiser, 2000; Rutter, 2002). Now the going gets really tough. Further progress in successfully treating complex disorders will increasingly depend on knowledge generated by additional branches of science that until just recently have been relegated to the sidelines of the life sciences. Molecular biology has shown that in the progression from genotype to phenotype (i.e., from initial gene expression to behavior), many levels of influence are introduced, each apparently operating by poorly understood dynamical operating rules (Strohman, 2002). This is surely a surmountable challenge, but it will require the integration and creation of new analytical models growing out of the disciplines of mathematics, statistics, kinetics, information technologies, and even thermodynamics (Strohman, 2002).

As we proceed along this bumpy road to human understanding, it is necessary to be reminded that parsimony does not refer to the simplest explanation possible but, rather, the simplest explanation that best fits the phenomenon under study. From time to time along this road, we will be pushed forward by the magic of serendipity—the human knack for making fortunate discoveries by accident. This remarkable tendency is perhaps the ultimate power of the human brain. In this case, it will be further empowered by our desire to lessen suffering of human beings and enhance their potential.

There are many other potholes on the road ahead as well. These include but are not limited to the following:

- The fragmentation of disciplines as a side effect of the need for deep specialization
- Becoming stuck in genocentric thinking; this is certainly an understandable tendency at present, but it is a self-limiting one as well
- The presence of painful, complex ethical dilemmas (there are many of these and they are not likely to recede)
- The opposing all too human perversities of destructive cynicism (e.g., "In the end, all of this

won't matter a bit") and gullible expectations (e.g., "The cure is just around the corner"); in fact, the latter can often precedes the former
- The struggle of translating research to practice (what is possible versus what "typically" happens haunts most fields of human endeavor)

So the road ahead will surely be full of potholes and at least temporary roadblocks. Fortunately, we possess a time-tested recipe for solving big, daunting, complex problems. We will need to stick to this basic recipe or else real progress will become increasingly difficult. Here it is:

1. Take one complex problem (autism or self-injurious behavior are good candidates).
2. Mix together with many potentially relevant disciplines.
3. Add a lot of good science and a pinch of creativity, passion, and serendipity.
4. Stir together.
5. Bake until thoroughly done. (WARNING: This may take a few decades or centuries.)
6. While baking, baste continuously with lots of money and talented, dedicated people.
7. When done, serve to a representative sample of those afflicted and record their reactions.
8. Repeat Steps 1–7 above until problem is solved.

History shows this recipe to have worked time and time again. One of its premises is that for the really tough problems, there are few short cuts. Furthermore, advances are driven by the problems themselves. The budget of the National Institutes of Health has been doubled in the past 5 years because of the tantalizing promise that real, meaningful human problems will be mitigated, maybe even solved in the years ahead. Some problems, perhaps fragile X syndrome will be one, may actually be cured within our lifetimes. With many other problems, treatments will surely improve, although ethically "acceptable" cures may remain elusive for the foreseeable future (Reinders, 2000).

The road ahead may be a series of frustrating dead ends caused by our inability to integrate our exploding knowledge of genetics and neuroscience with the behavioral sciences in meaningful ways. I see a different road, though, one that is long and strewn with potholes and detours but, nevertheless, a road on which we will make steady progress, resulting in improvements in the quality of life of people at-risk for and with intellectual and developmental disabilities, a road along which, ultimately, anything is possible.

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