Our Physiological Future

M.J. Joyner, MD

Department of Anesthesiology
Mayo Clinic
Rochester, MN
Not Provocative Enough?
Precision Medicine: Time For A 2\textsuperscript{nd} Opinion?

M.J. Joyner, MD

Department of Anesthesiology
Mayo Clinic
Rochester, MN
1st Some Definitions

- HGP = Human Genome Project
- SNP = Single Nucleotide Polymorphisms
  - Common DNA sequence variation within a population
- GWAS = Genome Wide Association Study
  - Are common DNA variants associated with a trait?
Overview of Talk

• Where did Genotype = Phenotype come from?
• Human Genome Project
• Genetic Revolution in Medicine
• Precision Medicine?
• Physiology & the “Way Out”?
A Brief History of Genotype = Phenotype
~1900 Mendel Rediscovered

First Generation

Yellow (yy)

Green (YY)

(Yy)  (Yy)

(Yy)  (Yy)

Second Generation

Green (Yy)

(Yy)  (Yy)

(Yy)  (yy)

Mary S. Gibbs (GNN)
What Happens Next 1.0?

- Johannsen – *Genotype & Phenotype*
- T.H. Morgan & Chromosomes
- Erwin Schrödinger “What is Life?”
- Watson & Crick Genes = DNA
- Definition of “What is a Gene” Shifts
- Ideas about the genotype phenotype relationship are unchanged
What Is A Gene?

But however far we may proceed in analysing the genotypes into separable genes or factors, it must always be borne in mind, that the characters of the organism—their phenotypical features—are the reaction of the genotype in toto. The Mendelian units as such, taken per se are powerless.

—Wilhelm Johannsen, 1923
The Central Dogma of Molecular Biology

- Medieval religious language
- “Code”
- Secret revealed
- Read-only information
- DNA = Phenotype is where various oversimplifications lead

What Happens Next 2.0?

- Sequence DNA on an industrial scale
- Link to phenotype
- Find common variants
- Do enough and missing heritability & soft inheritance are “solved”
- Engineer animal models & translate rapidly to cures
- Ignore Epidemiology & Physiology
HGP: Predictions from the 80s and 90s

“The sequence of the human DNA is the reality of our species.” Dulbecco 1986

“Sequencing the human genome is like pursuing the holy grail.” Gilbert 1991

“We will learn more about human development and pathology in the next twenty-five years than we have in the past two thousand.” Hood 1992

“If research support continues at vigorous levels, it is hard to imagine that genomic science will not soon reveal the mysteries of hereditary factors in heart disease, cancer, diabetes, mental illness, and a host of other conditions.”

-Collins 2001
Genetic Revolution in Medicine
Genetic Revolution in Medicine

Figure 1. Steps Involved in the Genetic Revolution in Medicine.

1. Disease with genetic component
   - Map
   - Clone gene

2. Diagnostics
   - Preventive medicine
     - Pharmacogenomics

3. Time

4. Gene therapy

5. Drug therapy

6. Accelerated by Human Genome Project

7. Cost savings

Collins NEJM 1999
1. Common Variant Hypothesis
Common Disease - Common Variant

Blood Pressure: 1mmHg Or Bust?

New Metric:
Genomic Futility Index (GFI)

\[ \frac{\text{# of authors}}{\text{effect size of biggest variant}} = \frac{400}{1\text{mmHg}} = 400 \]

Paneth, personal communication
2. Diagnostics: Risk Prediction
Risk Alleles & CV Disease Event Status
10-Year Follow-Up for the Genetic Risk Score (GRS)

101 SNP GRS

- CVD (n=634)
- No CVD (n=18,679)

12 SNP GRS

Type II Diabetes Risk

**Framingham Score +/- Gene Score**

1) Phenotype risk models better than gene scores

2) More genes don’t improve things!

3) Does it change advice to patients?

Diabetes: More Variants Same Story

Waist Circ Beats Sequencing: *Diabetes, HTN, & CVD*

3. Prevention
Behavior Change = Not Much

Personalized Genetic Risk Counseling to Motivate Diabetes Prevention

A randomized trial

RESULTS—The 108 participants enrolled in the diabetes prevention program included 42 participants at higher diabetes genetic risk, 32 at lower diabetes genetic risk, and 34 untested control subjects. Mean age was 57.9 ± 10.6 years, 61% were men, and average BMI was 34.8 kg/m², with no differences among randomization groups. Participants attended 6.8 ± 4.3 group sessions and lost 8.5 ± 10.1 pounds, with 33 of 108 (30.6%) losing ≥5% body weight. There were few statistically significant differences in self-reported motivation, program attendance, or mean weight loss when higher-risk recipients and lower-risk recipients were compared with control subjects (P > 0.05 for all but one comparison).

CONCLUSIONS—Diabetes genetic risk counseling with currently available variants does not significantly alter self-reported motivation or prevention program adherence for overweight individuals at risk for diabetes.
What About Smoking & Lung CA?

A Qualitative Study of Lung Cancer Risk Perceptions and Smoking Beliefs Among National Lung Screening Trial Participants

Attitudes and Perceptions About Smoking Cessation in the Context of Lung Cancer Screening

• Fatalism vs. I got lucky & am protected
• Did not motivate behavior change
• Limited studies on small effect size gene variants consistent with imaging studies

4. Pharmacogenomics & Targeted Therapy
Success in Breast CA?
Tamoxifen Metabolism and Breast Cancer Survival

Probability of relapse

Enhanced

Decreased

Follow-up (years)

0.0
0.1
0.2
0.3
0.4

Schroth et al: JAMA, 2009
On Further Review

Although CYP2D6 is a strong predictor of IDFS using strict inclusion criteria, because the results are not robust to inclusion criteria (these were not defined a priori), prospective studies are necessary to fully establish the value of CYP2D6 genotyping in tamoxifen therapy.

Conclusions: Despite a weak association between CYP2D6 genotype and surrogate endpoints for overall survival, we did not identify an association between CYP2D6 genotype and tamoxifen response for all-cause mortality or overall survival. The current evidence does not support the use of CYP2D6 genotyping to guide tamoxifen prescribing for the treatment of breast cancer.

Province et al Clin Pharm Ther 2014
Lum et al PLOS1 2013
**Results**

At 4 weeks, the mean percentage of time in the therapeutic range was 45.2% in the genotype-guided group and 45.4% in the clinically guided group (adjusted mean difference, [genotype-guided group minus clinically guided group], −0.2; 95% confidence interval, −3.4 to 3.1; P=0.91). There was no significant between-group difference among patients with a predicted dose difference between the two algorithms of 1 mg per day or more. There was, however, a significant interaction between dosing strategy and race (P=0.003). Among black patients, the mean percentage of time in the therapeutic range was less in the genotype-guided group than in the clinically guided group. The rates of the combined outcome of any INR of 4 or more, major bleeding, or thromboembolism did not differ significantly according to dosing strategy.

**Conclusions**

Genotype-guided dosing of warfarin did not improve anticoagulation control during the first 4 weeks of therapy. (Funded by the National Heart, Lung, and Blood Institute and others; COAG ClinicalTrials.gov number, NCT00839657.)
Why commercialization of gene therapy stalled; examining the life cycles of gene therapy technologies

FD Ledley¹,², LM McNamee¹, V Uzdil¹ and IW Morgan³

This report examines the commercialization of gene therapy in the context of innovation theories that posit a relationship between the maturation of a technology through its life cycle and prospects for successful product development. We show that the field of gene therapy has matured steadily since the 1980s, with the congruent accumulation of > 35,000 papers, > 16,000 US patents, > 1,800 clinical trials and > $4.3 billion in capital investment in gene therapy companies. Gene therapy technologies comprise a series of dissimilar approaches for gene delivery, each of which has introduced a distinct product architecture. Using bibliometric methods, we quantify the maturation of each technology through a characteristic life cycle S-curve, from a Nascent stage, through a Growing stage of exponential advance, toward an Established stage and projected limit. Capital investment in gene therapy is shown to have occurred predominantly in Nascent stage technologies and to be negatively correlated with maturity. Gene therapy technologies are now achieving the level of maturity that innovation research and biotechnology experience suggest may be requisite for efficient product development. Asynchrony between the maturation of gene therapy technologies and capital investment in development-focused business models may have stalled the commercialization of gene therapy.

Gene Therapy (2014) 21, 188–194; doi:10.1038/gt.2013.72; published online 5 December 2013

Keywords: innovation; technology life cycles; biotechnology; capital investment; drug development
6. Drug Therapy: **EROOM’S Law?**

- Overall trend in R&D efficiency (inflation-adjusted)

- FDA tightens regulation post-thalidomide

- FDA clears backlog following PDUFA regulations plus small bolus of HIV drugs

- First wave of biotechnology-derived therapies

Scannell et al. Nat Rev Drug Disc 2012
Eliminating the Suffering and Death Due to Cancer by 2015

Dr. Andrew von Eschenbach

Dr. Andrew von Eschenbach is the Director at the National Cancer Institute. This is an edited version of his remarks at a Center for Medical Progress forum on June 21, 2005.

• Genotype tumors
• Targeted therapy
• Bioinformatics
• Cure disease
• *Cited Lance Armstrong as proof of concept*
Targeted Therapy & Cancer

- Cancer is multi-clonal & adaptive
- Driver mutations
- Surrogate end points vs. Overall Survival
- Revenge of the resistant clones

However, we need to remember that these drugs also have toxic effects, they are enormously and inappropriately expensive, and they haven’t cured anyone yet. It is premature to be opening the victory champagne bottles.

Longo NEJM 2014
“In view of the absence of data from randomized trials, the clinical usefulness of large-scale genomic testing has not been formally shown. In the SHIVA trial, we aimed to assess whether histology-agnostic use of marketed molecularly targeted agents outside their indications based on tumor molecular profiling could improve outcomes for patients with any kind of cancer for whom standard of care had failed, compared with treatment at the physician's choice.”

- Advanced CA
- Targeted tx vs. usual care
- Agnostic to anatomy

Le Tourneau et al, Lancet Onc 2015
Figure Legend:

Oral Cancer–Free Survival (CFS) in Study Participants With Loss of Heterozygosity in the Erlotinib vs Placebo Study ArmsE/N indicates number of participants who experienced a cancer or death event/total number of participants; HR, hazard ratio.
What About Gleevec?

The “Moral” of the Gleevec Story

In a way, Gleevec is an exceptional case, and the same success is not likely to be achieved with other cancers any time soon. Unlike most other cancers, which are caused by a multitude of complex interacting genetic and environmental factors and therefore have many targets, CML is caused by a single aberrant protein related to a consistent chromosomal translocation. Scientists were thus able to focus all of their efforts on this single target. Nonetheless, the Gleevec story is no less an excellent and, some would say, beautiful example of how knowledge of the biological functioning of a cell can lead to life-saving medical treatment.

http://www.nature.com/scitable/topicpage/gleevec-the-breakthrough-in-cancer-treatment-565
“Mistakes Were Made”

HOPE IN THE LAB: A special report.; A Cautious Awe Greets Drugs That Eradicate Tumors in Mice

By GINA KOLATA
Published: May 3, 1998

Other scientists are not so restrained. "Judah is going to cure cancer in two years," said Dr. James D. Watson, a Nobel laureate who directs the Cold Spring Harbor Laboratory, a
Direct-to-consumer pharmacogenomic testing is associated with increased physician utilisation

Cinnamon S Bloss,¹ Nicholas J Schork,¹,² Eric J Topol¹,²,³

In conclusion, DTC PGx risk profiling among a selected sample of persons was associated with statistically significant increases in physician utilisation. PGx testing did not result in any short-term changes in psychological health. Further evaluation of the utility and cost considerations for DTC PGx testing appear to be warranted.
8. Don’t Forget……

• The Incidentalome
• Genetic Purgatory
Suppose there is a panel of genomic tests, each with superb testing performance: a sensitivity of 100% and a false-positive rate of 0.01%. That is, of 100,000 individuals, each test will only produce 10 false-positive results. Assuming a disease prevalence of 1 in 100,000, in a population of 100,000 the number of true-positive results will increase by 1 with each additional test. The increase in the number of false-positive results will be 10 with each independent test, but some individuals will be subject to multiple false-positive results; therefore, the increase of the number of individuals with a false-positive result will be slightly less than 10 per test. The Figure shows the increase in the proportion of individuals with a false-positive test result under these assumptions. As illustrated, with 10,000 independent tests, more than 60% of the entire population tested would have false test results.

Kohane et al JAMA 2006
Merriam-Webster's defines purgatory as "an intermediate state after death for expiatory purification" or more specifically as "a place or state of punishment wherein according to Roman Catholic doctrine the souls of those who die in God’s grace may make satisfaction for past sins and so become fit for heaven." Alternatively, it is defined as "a place or state of temporary suffering or misery."

Either way, purgatory is a place where you are stuck, and you don't want to be stuck there. It is in this context that the term genetic purgatory is introduced. Genetic purgatory is a place where the genetic test-ordering physician and patients and their families are stuck when a variant of uncertain/unknown significance (VUS) has been elucidated. It is in this dark place where suffering and misery are occurring because of unenlightened handling of a VUS, which includes using the VUS for predictive genetic testing and making radical treatment recommendations based on the presence or absence of a so-called maybe mutation. Before one can escape from this miserable place, one must first recognize that one is stuck there. Hence, the purpose of this review article is to fully expose the VUS issue as it relates to the cardiac channelopathies and make the cardiologists/geneticists/genetic counselors who order such genetic tests believers in genetic purgatory. Only then can one meaningfully attempt to get out of that place and seek to promote a VUS to disease-causative mutation status or demote it to an utterly innocuous and irrelevant variant.
Precision Medicine: What’s New?

- “P4 Medicine” Zerhouni
- Multiple prior initiatives
- Collins Nature 2004

The case for a US prospective cohort study of genes and environment

Francis S. Collins
“And that’s why the budget I send this Congress on Monday will include a new Precision Medicine Initiative that brings America closer to curing diseases like cancer and diabetes, and gives all of us access, potentially, to the personalized information that we need to keep ourselves and our families healthier.”

President Barack Obama
January 30, 2015
Targeted Research & Big Science?

“It's like Deja-vu, all over again.”

-Yogi Berra
Presidents need to show more interest in what the specific results of research are in their lifetime, and in their administration. A great deal of basic research has been done but I think the time has come to zero in on the targets by trying to get our knowledge fully applied.

We must make sure no life saving discovery is locked up in the laboratory.
The War on Cancer: 
Targeted Research Meets Big Science

Meanwhile, Back At The Ranch....
Physiology & the “Way Out”?
Development
To create the targeting vector, Dr. Tomas A. Prolla (University of Wisconsin, Madison) isolated a mouse DNA polymerase γ (Polg) DNA sequence and used site-directed mutagenesis to introduce an AC-->CT two-base substitution corresponding to positions 1054-1055 in exon 3. ........

Safdar et al. PNAS, 2011.
Decline in Deaths from CV Disease

Better living through plumbing, electricity, traditional drug development & clinical trials?

Looks like Physiology to Me!

Adapted from Nabel & Braunwald NEJM 2012
Regenerative Medicine
Cell Therapy vs. Exercise Training in CHF

Joyner Criteria:
Regenerative Medicine enthusiasts can declare victory when the effects of stem cells on EF = the effects of exercise training.

- Cell therapy:
  - Traverse et al JAMA 2012
  - Perin et al JAMA 2012

- Exercise:
  - Wisloff et al Circ 2007
  - Erbs et al Circ HF 2010
β-Blockers for CHF

Ejection Fraction (%)

**Standard therapy**
- BSLN
- Day 1
- 1M
- 3M

**Metoprolol**
- BSLN
- Day 1
- 1M
- 3M

P = 0.013 for Metoprolol vs Standard therapy

P < 0.0001

P < 0.05

Eichhorn et al Circulation 1996
BP & Women
Fainting: Women vs. Men

Hypertension & Sex in Humans

• Blood pressure and the prevalence of hypertension increases with age

• Women “protected” until age of menopause
Young Women & NE (NA)

Closed Circles = Placebo  Open Circles = Propranolol

Hart et al J Physiol 2011
Vascular Transduction

A

B

Slope = transduction measure
“For many problems there is an animal on which it can be most conveniently studied.”

Named by Hans Krebs in 1975
Genetic Revolution in Medicine

Figure 1. Steps Involved in the Genetic Revolution in Medicine.

1. Disease with genetic component
   - Map
   - Clone gene

2. Diagnostics
   - Preventive medicine
     - Pharmacogenomics

3. Time

4. Gene therapy

5. Drug therapy

6. Accelerated
   - by Human Genome Project

7. Cost savings
Curb Your Enthusiasm?

1. Common Disease-Common Variant Hypothesis rejected
2. Diagnostics: risk prediction not improved
3. Prevention: behavior unchanged
4. Pharmacogenomics trials: failed
5. Still “waiting” for gene therapy
6. Pharma pipeline is “dry”
7. Cost savings unlikely

Collins 2010 -- “My job, it seems to me, is not to spend my time apologizing for being optimistic.”
Areas of Utility?

- Rare diseases
- Drug targets?
- Microbes
- Animal models?

Red Blood Cell Transfusion
Precision vs Imprecision Medicine

Current transfusion guidelines, though well-intentioned are admittedly deficient. The objectives of reducing exposure to allogeneic blood and conserving a precious resource, however commendable, fall short of the ultimate goal: improving patient outcomes. Precision in the personalized matching of red blood cell units is gradually being embraced. A similar degree of precision should apply to administration of these products.
Biological Version Of McNamara’s Fallacy?

1. Measure whatever can be easily measured.

2. Disregard that which cannot be measured easily.

3. Presume that which cannot be measured easily is not important.

4. Presume that which cannot be measured easily does not exist.

5. **Focus strategic, tactical, and management efforts on # 1.**
Closing Thoughts
Three Stages of Insight

- **Beginning**: “we know nothing”
- **Hazard**: “We know a lot”
- **Insight**: “we know nothing”
- **Expertise**: “How much we actually know”
- **How much we don’t know**: “How much we think we know”

*Simon Wardley*
“Reductionism in biology merely replaces one type of complexity by a different kind of complexity.”

“In the 21st Century we will see the progressive triumph of physiology over molecular biology.”
Discussion:

*Is This a Private Fight or Can Anyone Join?*
What if I am Wrong?
Cancer: Will Individual Successes Drown in a Sea of Obesity?

Type of Cancer and BMI

Men
- Prostate (≥35)
- Colon and rectum (≥35)
- Liver (≥35)

Relative Risk of Death

Women
- Liver (≥35)
- Breast (≥40)
- Uterus (≥40)

Blood Pressure of Identical Twins

Blood pressure of the other twin (mmHg)

Blood pressure of 1 identical twin (mmHg)

- Systolic
- Diastolic

Smirk F. H. High Arterial Pressure. 1957.
Blood Pressure vs. Culture

Physiology vs. Twin Studies

“Civilizations die from suicide, not by murder…..”

Toynbee
PROGRESS AGAINST CANCER?

John C. Bailar III and Elaine M. Smith

Abstract We assessed the overall progress against cancer during the years 1950 to 1982. In the United States, these years were associated with increases in the number of deaths from cancer, in the crude cancer-related mortality rate, in the age-adjusted mortality rate, and in both the crude and the age-adjusted incidence rates, whereas reported survival rates (crude and relative) for cancer patients also increased.

In our view, the best single measure of progress against cancer is change in the age-adjusted mortality rate associated with all cancers combined in the total population. According to this measure, we are losing the war against cancer, notwithstanding progress against several uncommon forms of the disease, improvements in palliation, and extension of the productive years of life. A shift in research emphasis, from research on treatment to research on prevention, seems necessary if substantial progress against cancer is to be forthcoming. (N Engl J Med 1986; 314:1226-32.)
US Death Rate 1969-2013

Ma et al JAMA 2015
Determinants of Health

- Behavior: 50%
- Environment: 20%
- Genetics: 20%
- Access to Care: 10%

CDC 2000
>240 AD Drugs Failed between 2002-2012

Only 1 received FDA approval

0.4% Success Rate
Alzheimer’s & Failed Reductionism

- Obsession with amyloid and tau
- Many pieces of data don’t fit the picture
- Epidemiology says AD has a big vascular component
- Engineer animal models based on amyloid and tau
- Treat the animals, early success, fail to translate, repeat….

What is needed? A model with modest over production of amyloid and tau with concurrent diabetes, hypertension, and lipid abnormalities…
Public Health Still Matters

Risks leading to death in perspective

- high blood pressure
- smoking
- high cholesterol
- obesity
- war
- pregnancy & birth
- medical complications
- murder
- illicit drug use
- transport accidents
- non-transport accidents
- infections
- alcohol
- physical inactivity
- low fruit and vegetables

National Health Service, UK.
PA & Longevity in ~650,000 Adults

Hazard ratio of mortality vs. years of life gained with leisure time physical activity (MET-hr/wk). Guidelines About Here.

Convergent Evolution:
Don’t Confuse Genotype & Phenotype


http://2.bp.blogspot.com
But Cancer *Is Different*

- CVD is a “single” disease
- Amenable to anatomical & engineering “fixes”
- Cancer is a complex multi-factorial collection of diseases…..
- Comparison is unfair
- *Justification of failed approach?*
  
  *Our strategy was good*
  
  *The problem not solvable with current tools*
- *Maybe -- but isn't this also a potential cognitive trap*
The Lung Cancer is Genetic Argument

- Smoking is a behavior driven by genes
- 90% of lung CA cases are in smokers
- Not all smokers get lung CA, so it must be smoking plus genes
- If we know the genes that “cause” people to smoke, and the genes that cause lung CA in some people then we can come up with drugs that either pre-empt people from smoking and/or treat lung CA
- *I am not kidding..... This chain of reasoning has been advanced.*
Japan: Height at Age 20

Stature (cm)

Year of birth

Males

Conscripts

Females

General population

Digital Human Research Center.
National Institute of Advanced Industrial Science and Technology.
Precision Medicine: Naming or Branding?

Conferring disciplinary status on such a loose basis might seem problematic. It reflects scientific practice, however, in which achieving disciplinary status is a matter of assertive rhetoric, social recognition, and appeal to funders. There certainly needs to be a basis of practice and achievement on which to hang the name, but the name works almost as a marketing tool. The advertising industry operates entirely on the strength of this recognition, but what is a little surprising is that such strategies appear to have developed in the sciences even as early as the first decade of the twentieth century.

Powell et al Hist Phil Life Sci 2007
Darwin & Natural Selection

- Parallels with artificial selection and plant and animal breeding
- Predates ideas about genes
- Observational
- What causes the variation?
- Panggenesis & Gemmules
Francis Galton 1822-1911

- English polymath
- Darwin’s cousin
- Weather maps, fingerprints, digital image analysis
- Biometrics, including height and intelligence
- Statistics
- Eugenics
- Arguments anticipate current discussions
Adapted from: Galton (1889). Natural Inheritance, pages 96 and 208.
Continuous Variation

NHANES 2007-2008, Age 40-49 yrs

Adapted from: NHANES 2007-2008.
Biometrics vs. Mendel

- Populations show continuous variation
- Plant results show clear distributions
- How to reconcile?
1919 Fisher “Reconciles” Heritability & Genes

- Current GWAS-based models ~ 20%
- Heritability estimates ~ 60-80%

Darwin – Galton – Mendel
Darwin & Natural Selection

Natural selection is Darwin’s most famous theory; it states that evolutionary change comes through the production of variation in each generation and differential survival of individuals with different combinations of these variable characters. Individuals with characteristics which increase their probability of survival will have more opportunities to reproduce and their offspring will also benefit from the heritable, advantageous character. So over time these variants will spread through the population.

Sit & Rise: A Human Bioassay?

1st Some Definitions

• HGP = Human Genome Project
• SNP = Single Nucleotide Polymorphisms
  Common DNA sequence variation within a population
• GWAS = Genome Wide Association Study
  Are common DNA variants associated with a trait?
• Myth = traditional story or a widely held but false belief or idea
Purposes of Mythology

- **Metaphysical** -- *Awakening a sense of awe before the mystery of being*
- **Cosmological** -- *Explaining the shape of the universe*
- **Sociological** -- *Validate and support the existing social order*
- **Pedagogical** -- *Guide the individual through the stages of life*

J. Campbell
Susser’s Data Confidence Rule: 

*Big Data & EMRs?*

Your confidence in any dataset increases by the square of your distance from it.
How Tall Are You: The Answer Is?

GWAS: Many Variants Small Effects

Notice what you like doing.
Do a lot of it.
Find a way to get paid doing it.
“Everybody sort of stepped back and said, ‘Okay, we really have to consider, now that gene therapy has lost its innocence, what are we doing here? And what are the ways in which, if we’re going to do additional experiments, we don’t let this happen again?’” Francis Collins, director of the National Institutes of Health, said recently. “It was big; it was very big. I would not be surprised if some young scientists who were thinking of going down this path decided to do something else.”
One little girl who has CF certainly made that assumption when she wrote the following in her diary on the day the CF gene was cloned, August 25, 1989: “Today is the most best day ever in my life. They found a jean [sic] for cystic fibrosis,” she wrote. But let’s look carefully at what underlies that assumption. Was the little girl right to have that kind of optimism? Here we are in 1997, eight years later, and the management of her disease has not changed in any significant way by finding the gene (although, fortunately, she’s doing pretty well). But I will predict that in the course of the next 10 years, management of CF will change. Already several new ideas are emerging about how to treat the disease, ideas that are based on our understanding of how the gene works. The healthy form of the gene itself may even be used in so-called gene therapy.