Advances in gene therapy and gene transfer: new directions and some regulatory challenges

T. Friedmann, MD

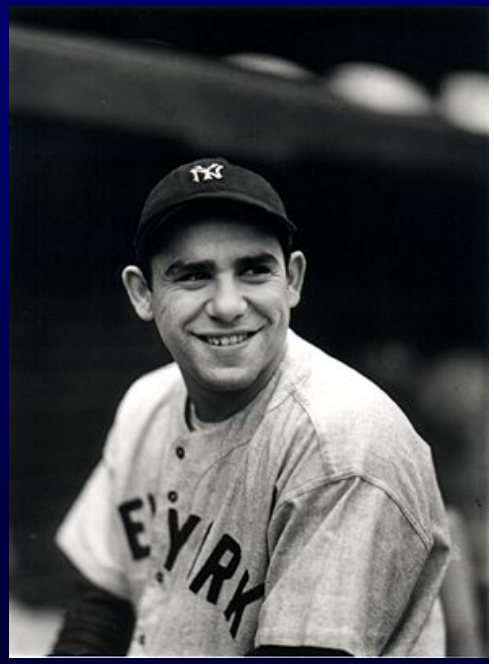
OBA IBC Conference

Washington, June, 2009

Prediction is very hard…especially regarding the future

Niels Bohr

Yogi Berra

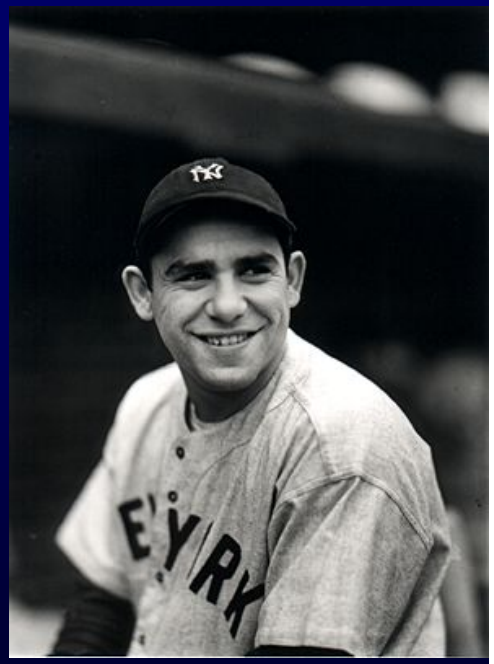


Prediction is very hard…especially regarding the future

Drew Endy

Niels Bohr

Yogi Berra



Gene therapy – issues relevant to IBC oversight

- Current technology and clinical application
- Developing technology – efficacy and safety
- Impending potential non-disease applications

Gene therapy – issues relevant to IBC oversight

- Current technology and clinical application
- Developing technology – efficacy and safety
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somatic cell

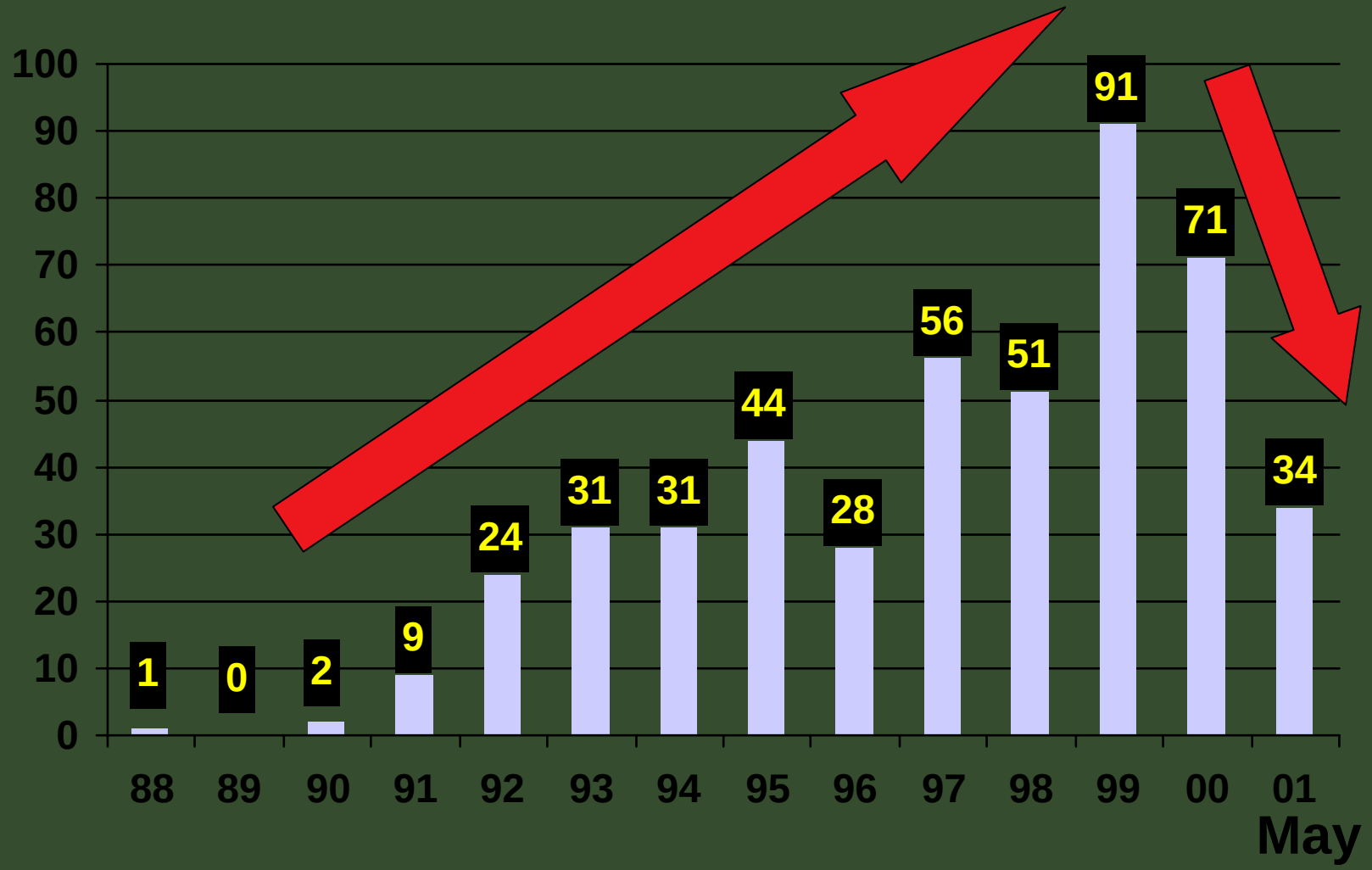
- therapy
- enhancement

germ cell

- therapy
- enhancement

LeRoy Walters
Kennedy Institute, Georgetown

Gene Transfer Trials by Year



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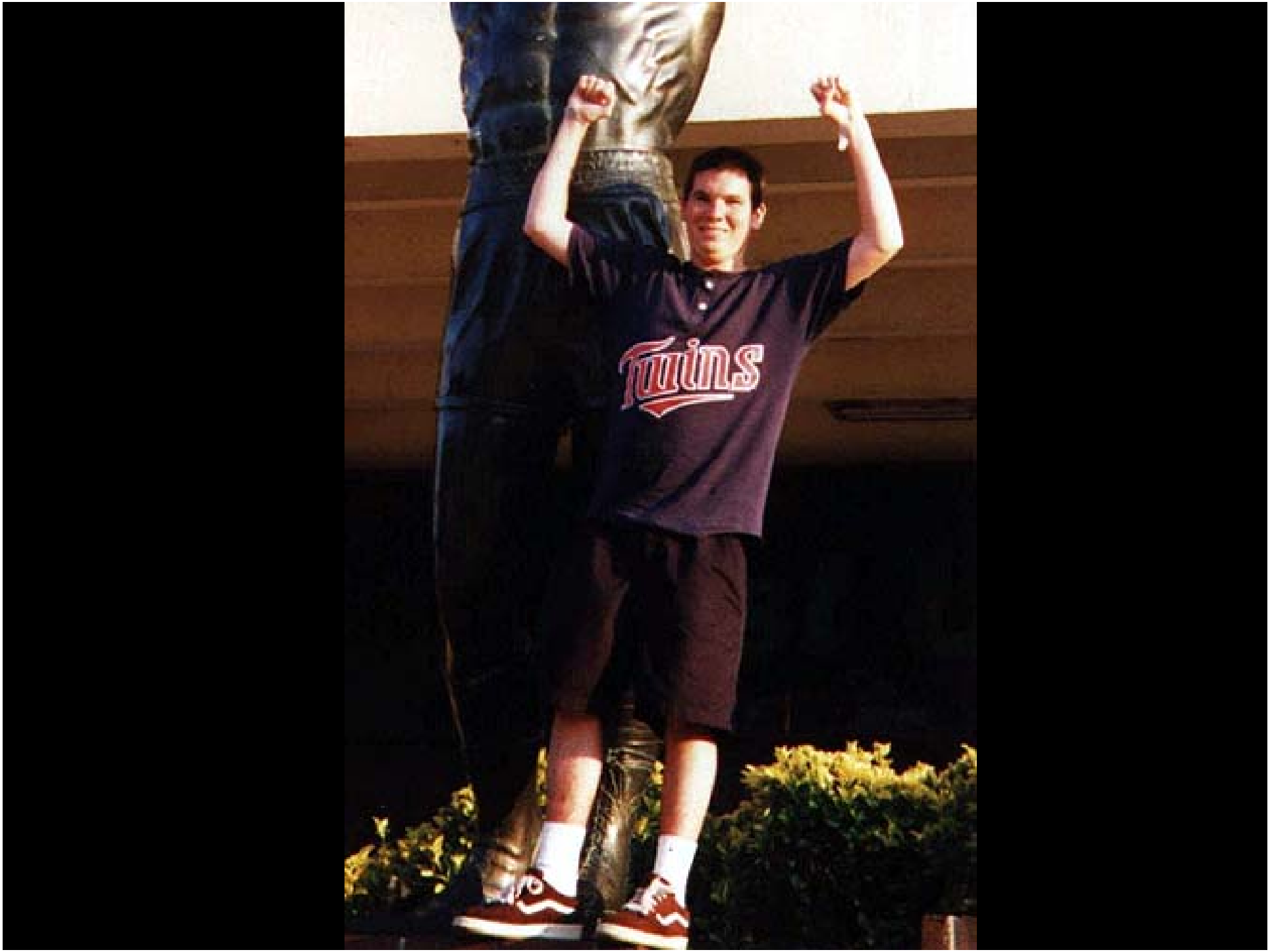
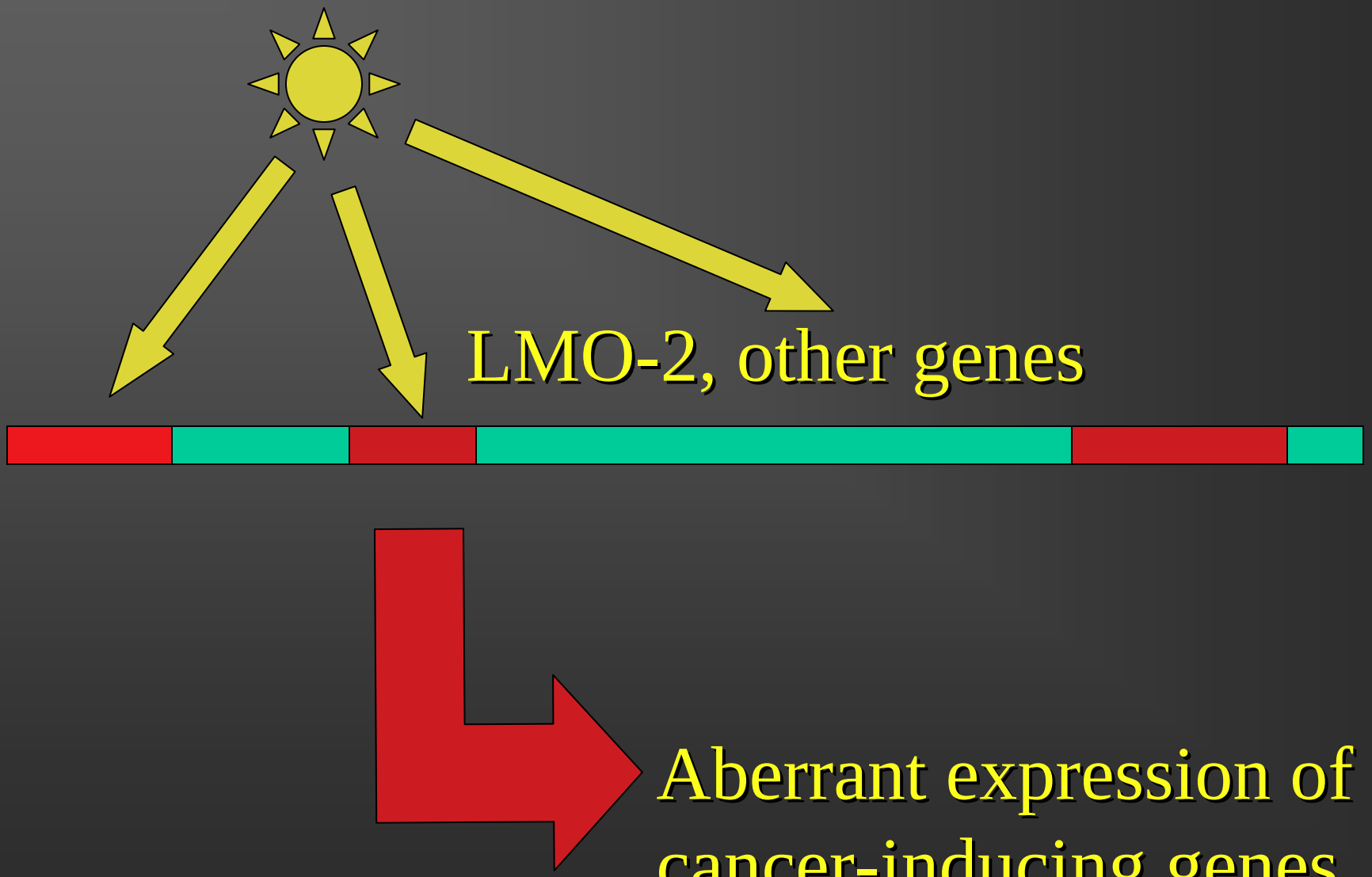

Twins

The first major success - SCID

At a cost

- Most X-SCID patients immunologically corrected
- Most are well and leading normal childhood lives>7-8 years after therapy,
- But 5 cases of leukemia as direct result of the treatment. One death

Insertional mutagenesis with retrovirus vector



ADA-SCID

- Similar clinical picture as X-SCID
- Most treated children show complete immune correction
- No leukemias
- Gene therapy is certainly therapy – improves lives of patients
- Arguably, close to being “standard of care”

A reminder from X-SCID gene therapy

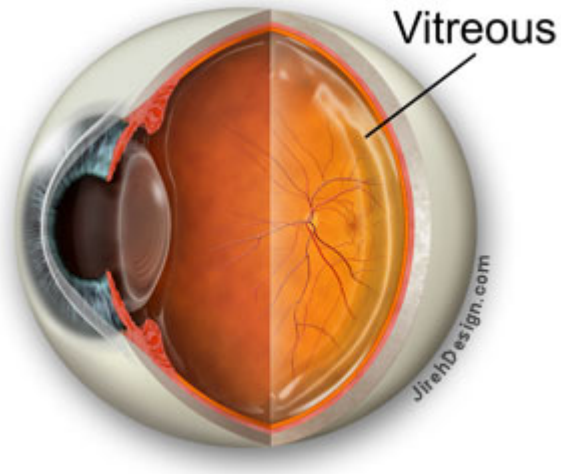
- Successful therapy is not defined by perfection or lack of risk and even known harm
  - Established cancer therapies often induce new cancers
  - Bone marrow transplantation still has high morbidity and mortality rate

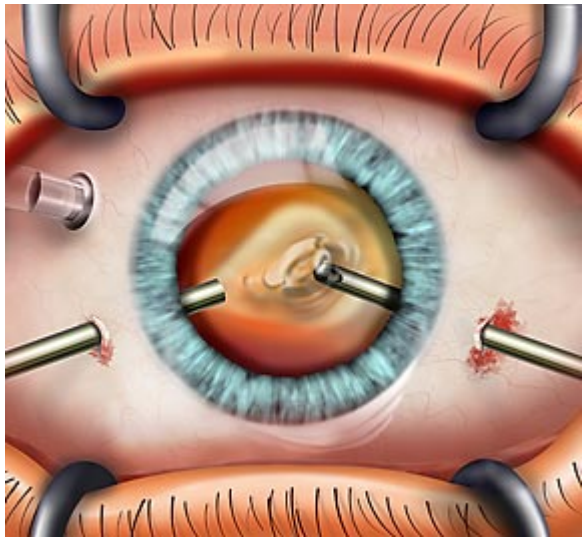
A reminder from X-SCID gene therapy

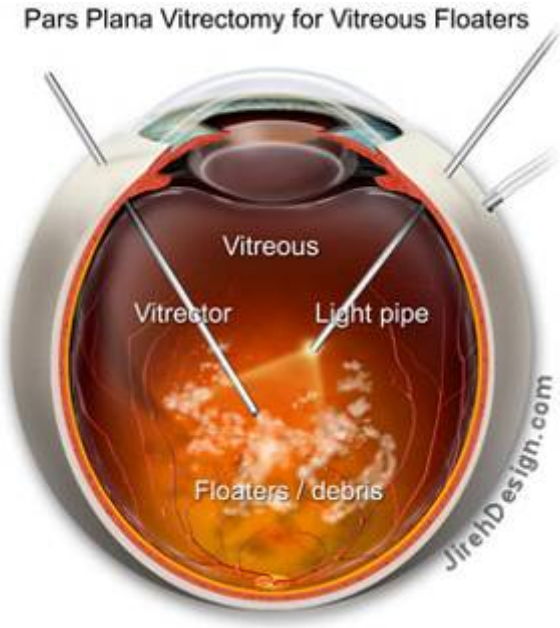
- Takes 2-3 decades for many new forms of therapy to become efficient, accepted and broadly used core treatments in Medicine
  - Bone marrow transplantation
  - Cancer chemotherapy

Leber's Amaurosis

- Genetic defect in essential protein (RPE65) in photoreceptors of retina
- Progressive severe blindness beginning early in childhood
- AAV virus vector delivery of normal gene directly to retina





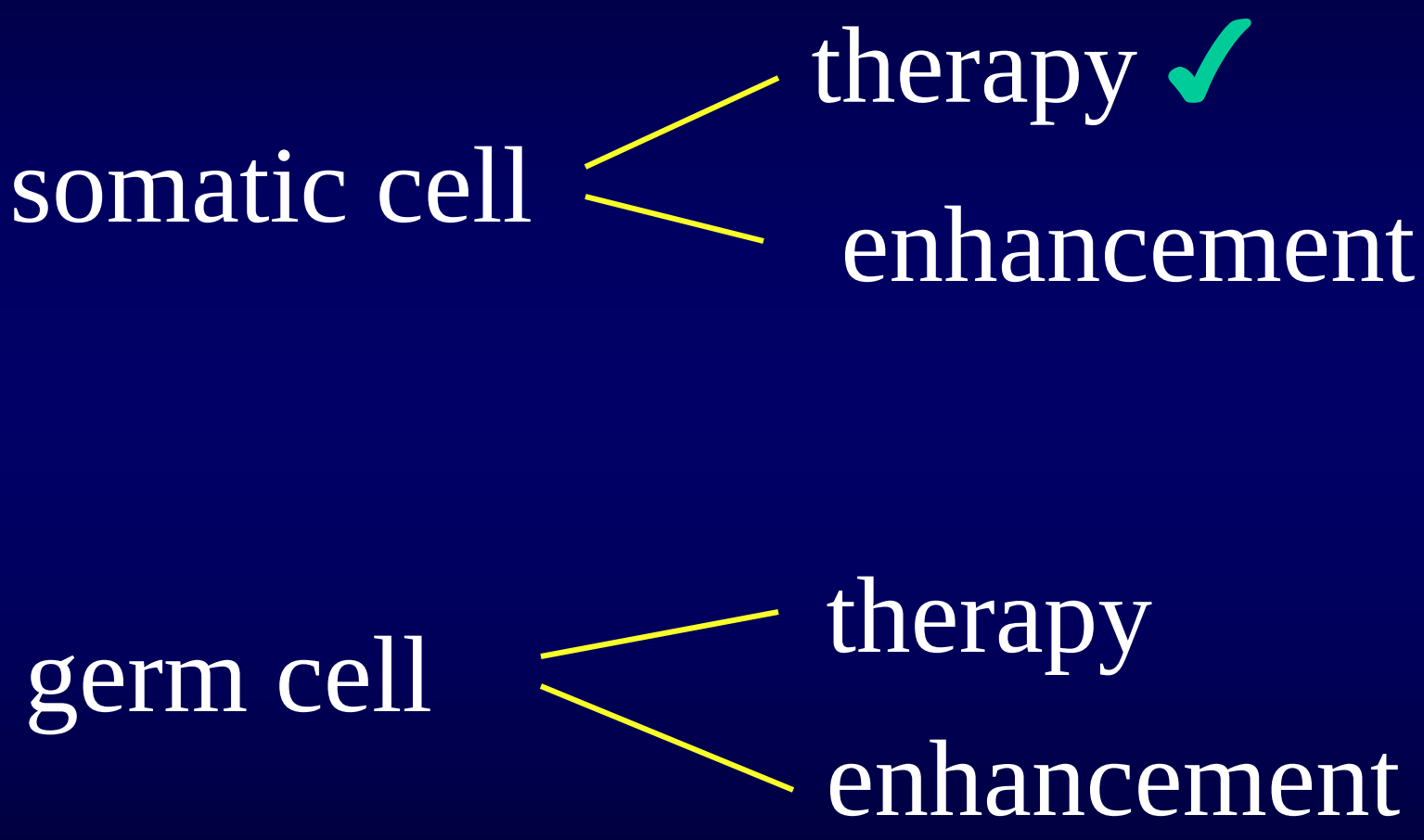


http://www.maculacenter.com/EyeSurgery/Vitrectomy.htm

Subretinal Injection of Recombinant Adeno-Associated Virus Vector 2.hRPE65v2 in Patient 2

OTHER DISEASES

- CANCER – melanoma, lung, head and neck, neuroblastoma, others
- NEUROLOGICAL DISEASE – adrenoleucodystrophy, Parkinson's
- MUSCLE DISEASE
- ARTHRITIS – rheumatoid arthritis



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Kennedy Institute, Georgetown

Gene therapy – issues relevant to IBC oversight

- Recent clinical successes
- Developing new technology – what effects on efficacy and safety?
- Non-disease applications

Regenerative stem cell-based methods

- Embryonic or adult stem cells, induced pluripotent stem cells (iPSC)
- Great clinical promise for clinical genetically modified cells
- But great pressure for premature clinical use and shortcuts – will recapitulate experience of GT. Needs alert oversight

RNA interference

- Non-vector, non-replicating synthetic RNAi, microRNAs
  - are they gene therapy?
  - is their safety established well enough to be exempt from NIH oversight or encompassed in revised NIH Guidelines (Fed.Reg. 4 March 2009)

RNA interference

- microRNA and siRNA – clinical trials for macular degeneration, liver cancer, heart failure, RSV infection, malaria
- Requires highly specific targeting – likelihood of “off target” effects
- Little known about toxicity of delivery materials (e.g., lipid nanoparticles, etc.)

Solutions to current technical problems

- Prevention of insertional mutagenesis
- Zinc finger-modified integrating vectors
- Specify safe site for integration of vector – “safe harbor” vectors

ZFP Transcription Factors

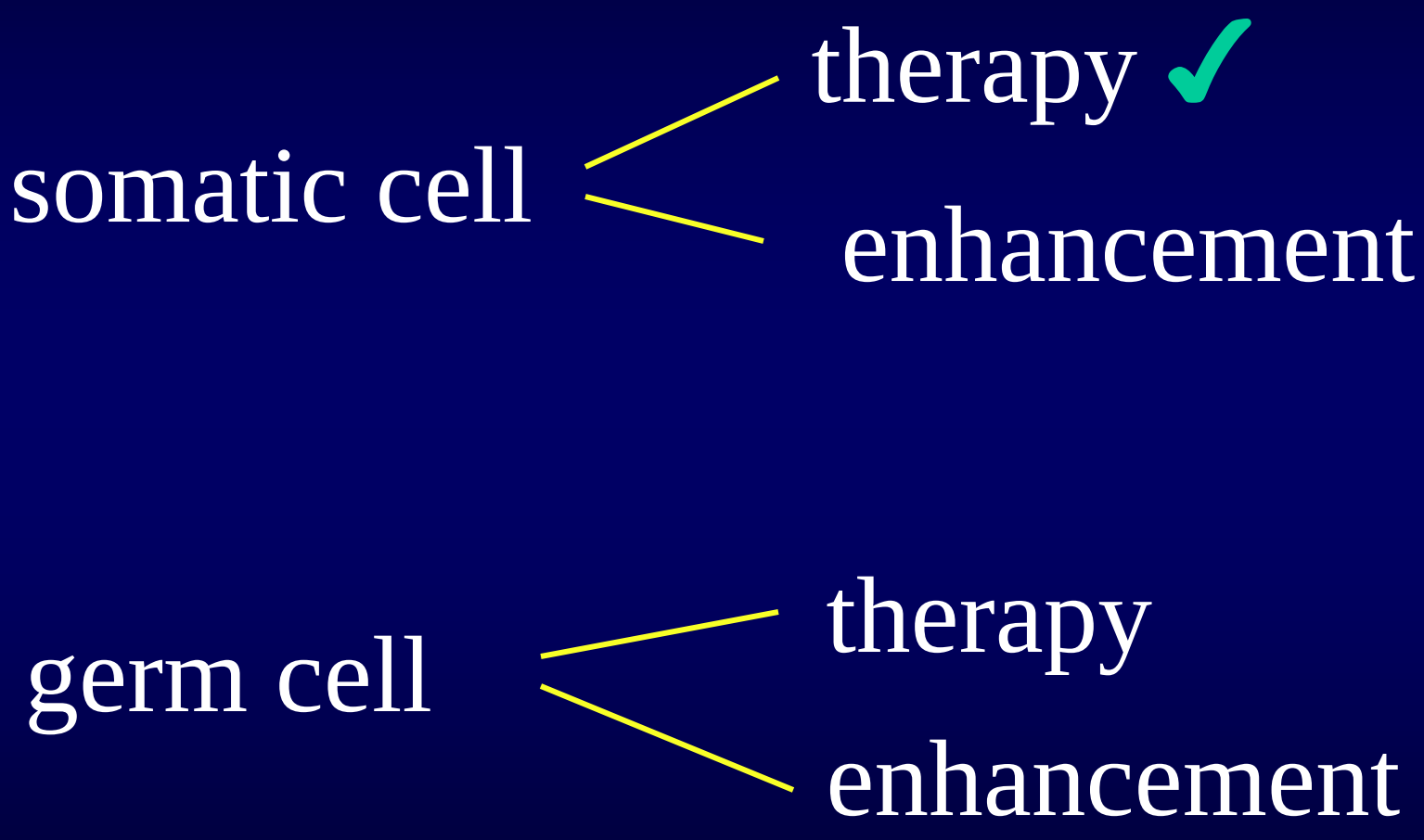
Zinc Finger DNA Binding Protein (ZFP)

- Activation - VP16
- Repression
- Cleavage

Sangamo BioSciences

Gene therapy – issues relevant to IBC oversight

- Recent clinical successes
- Impending new technology
- Are non-disease applications coming?



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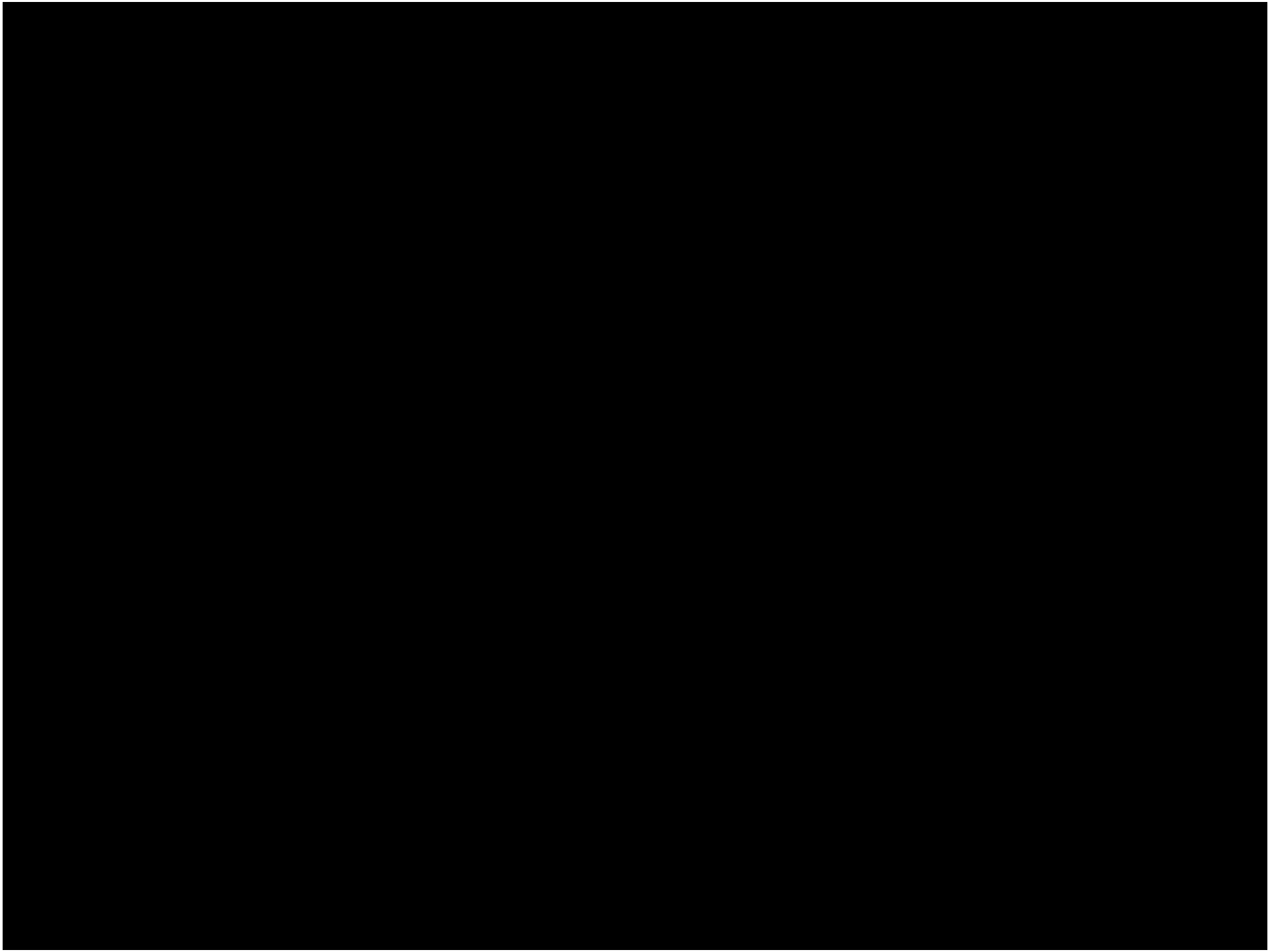
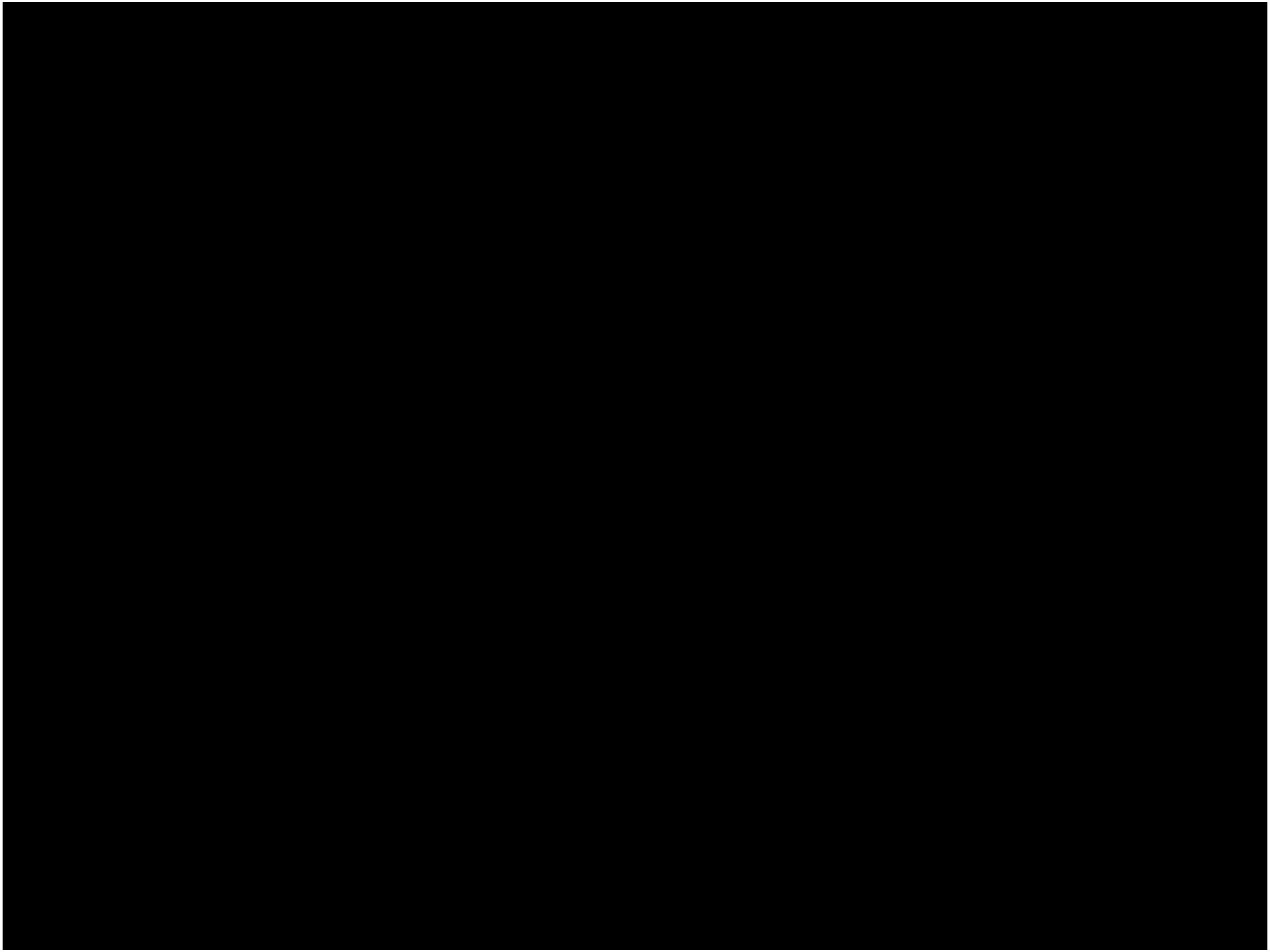
IBC dilemmas in genetic enhancement

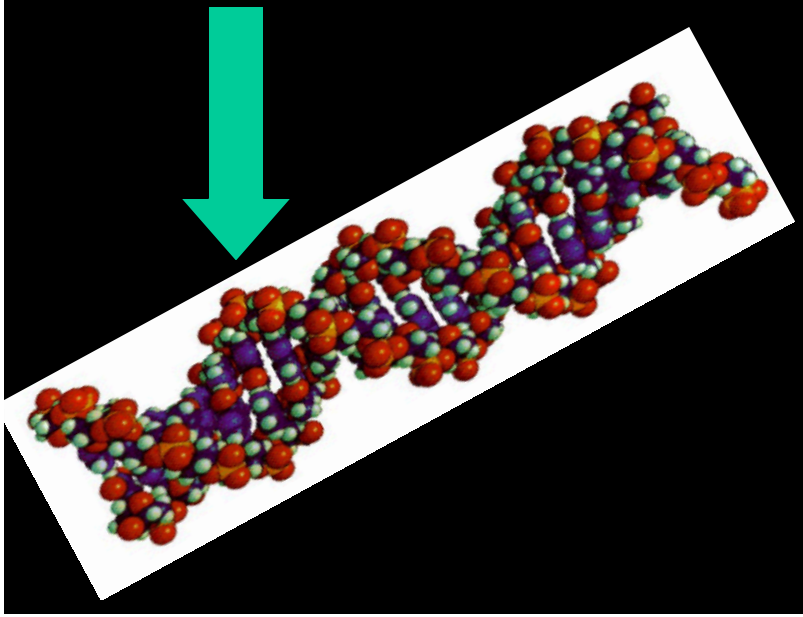
- Inexorable shift from clear therapy to modification of “normal” traits
- Boundary between disease and enhancement can be blurred; i.e., muscle degeneration during “normal” aging
- Are safety compromises in the name of therapy also acceptable in enhancement setting? Impending challenge to IBC committees.

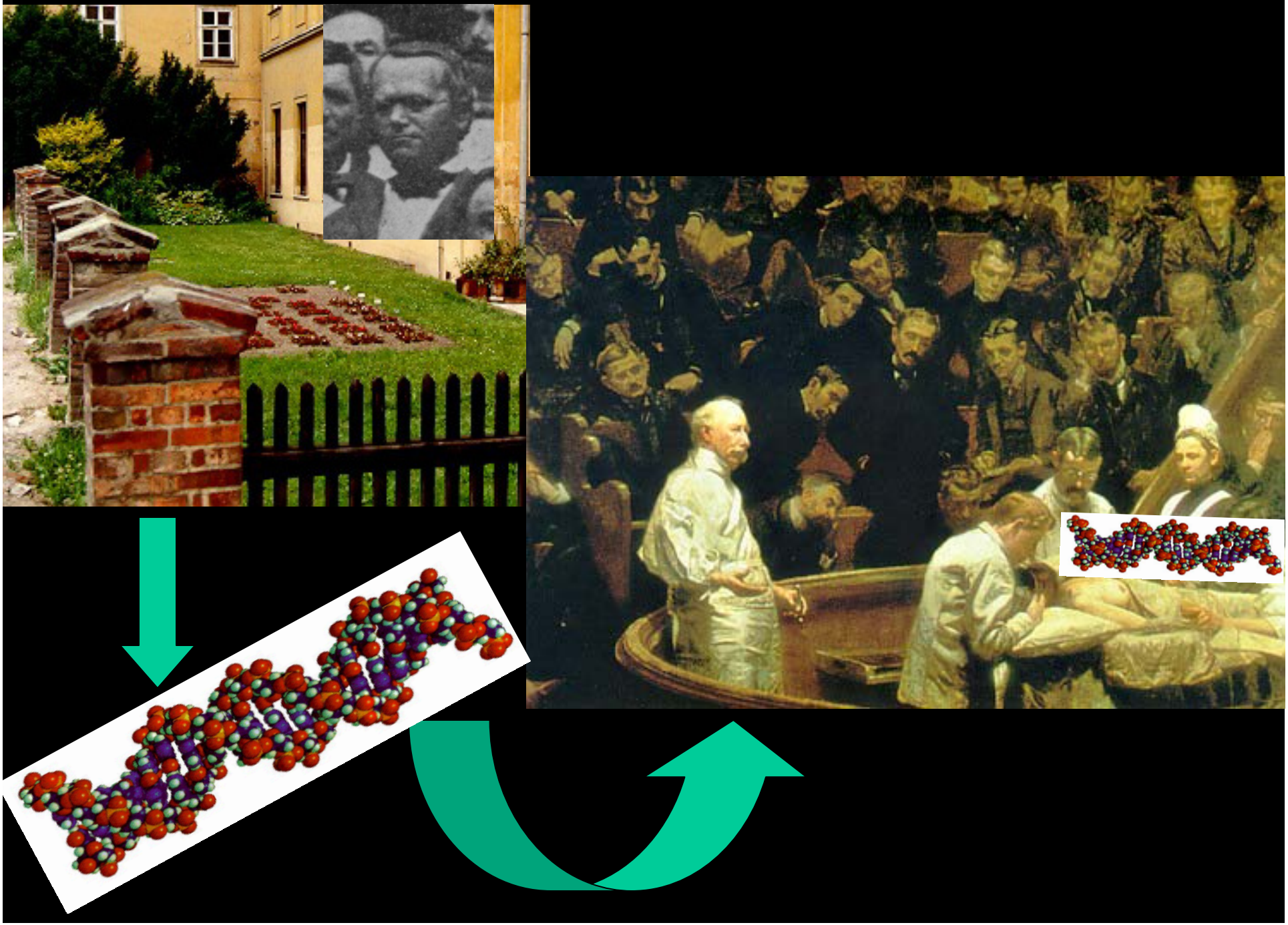
SUMMARY

- Complex new technologies will increasingly be applied to human biology and to new therapies
- Highly promising, but often unpredictable and potentially risky
- If true to form, there methods will require decades for efficient and safe application
- Require transparent oversight – continued good work from IBCs









David Vetter 1971-1983

Gene therapy – issues relevant to IBC oversight

- Recent clinical successes
- Impending new technology
- Non-disease applications

Gene therapy – a reality

- Difficult birth - initial exaggerated expectations, early setbacks and serious adverse events
- Recent successes – establish proof of concept, therapeutic benefit

X-linked Severe Combined Immunodeficiency Disease (X-SCID)

- mutations in gene for common gamma chain of interleukin receptors
- combined T- and B-cell deficiency
- life-threatening infections - early death
- definitive therapy - bone marrow transplantation
- otherwise, only symptomatic treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

BRIEF REPORT

◄ Previous Volume 358:2240-2248 May 22, 2008 Number 21 Next ►

Safety and Efficacy of Gene Transfer for Leber's Congenital Amaurosis

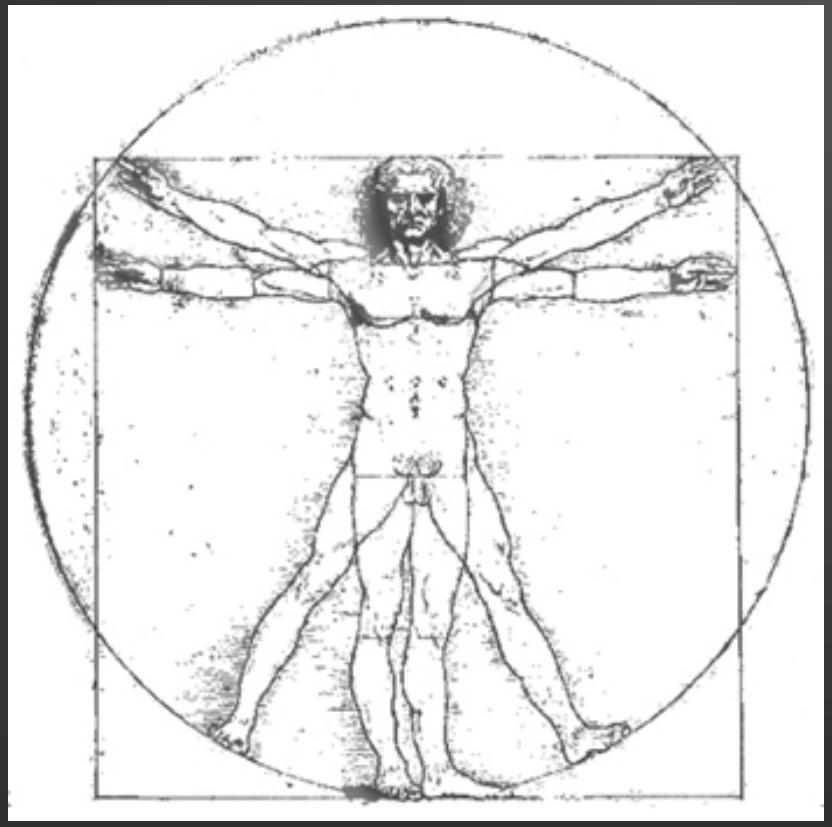
Albert M. Maguire, M.D., Francesca Simonelli, M.D., Eric A. Pierce, M.D., Ph.D., Edward N. Pugh, Jr., Ph.D., Federico Mingozzi, Ph.D., Jeannette Bennicelli, Ph.D., Sandro Banfi, M.D., Kathleen A. Marshall, C.O.T., Francesco Testa, M.D., Enrico M. Surace, D.V.M., Settimio Rossi, M.D., Arkady Lyubarsky, Ph.D., Valder R. Arruda, M.D., Barbara Konkle, M.D., Edwin Stone, M.D., Ph.D., Junwei Sun, M.S., Jonathan Jacobs, Ph.D., Lou Dell'Osso, Ph.D., Richard Hertle, M.D., Jian-xing Ma, M.D., Ph.D., T. Michael Redmond, Ph.D., Xiaosong Zhu, M.D., Bernd Hauck, Ph.D., Olga Zelenaia, Ph.D., Kenneth S. Shindler, M.D., Ph.D., Maureen G. Maguire, Ph.D., J. Fraser Wright, Ph.D., Nicholas J. Volpe, M.D., Jennifer Wellman McDonnell, M.S., Alberto Auricchio, M.D., Katherine A. High, M.D., and Jean Bennett, M.D., Ph.D.

How is clinical gene therapy doing?

II. New and Imminent Technology

- Embryonic stem cells and induced pluripotent stem cells (iPS)
- Vulnerable to same problems as early gene therapy
  - *–Fast-tracked, un-rigorous,*
  - *–Exaggerated expectations, claims*
  - *–Pressure for premature clinical trials*

Enhancement - making us “better than normal”, ideal



Vitruvian man - reflection of nature’s symmetry and perfection

Therapy vs. enhancement?

- No clear line between therapy and enhancement – what is normal and what is disease?
  - *intelligence and cognition - what is normal, ideal*
  - *beauty - whose concept of beauty?*
- health or disease
  - *is all depression pathological, require therapy?*
  - *memory deficit in Alzheimer's disease. When does "I forgot where I put my keys" become "I forget where I live"*
  - *muscle wasting in aging, etc. - normal or disease, require treatment?*

Some enhancement is socially and ethically acceptable, justifiable

- cosmetic surgery - spectrum from lipoplasty, botox and breast implants to congenital malformations
- therapy of serious psychiatric disease and “deviant” behavior
  - *antidepressants, tranquilizers, mood enhancers*
  - *Ritalin for attention deficit hyperactivity disorder, etc.*
- social and recreational drug use - mood and performance-enhancing
  - *alcohol, caffeine, marijuana, cocaine, etc.*

The line between therapy and enhancement can become blurred


6/27/07
before
9/9/07
after

ARCH DEVELOPMENT FOLLOWED BY THE MYOBRACE™

1 START OF TREATMENT

» 3 AUGUST 2004

START

» 3 AUGUST 2004

2 BENT WIRE SYSTEM TREATMENT COMPLETE

» 8 FEBRUARY 2005

BWS

» 8 FEBRUARY 2005

3 AFTER SIX WEEKS OF DAILY MYOBRACE™ USE.

» 22 MARCH 2005

myobrace

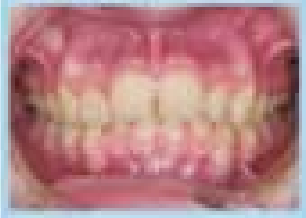
» 22 MARCH 2005

CROWDING

TYPICAL CASE SELECTION

CLASS II

TYPICAL CASE SELECTION

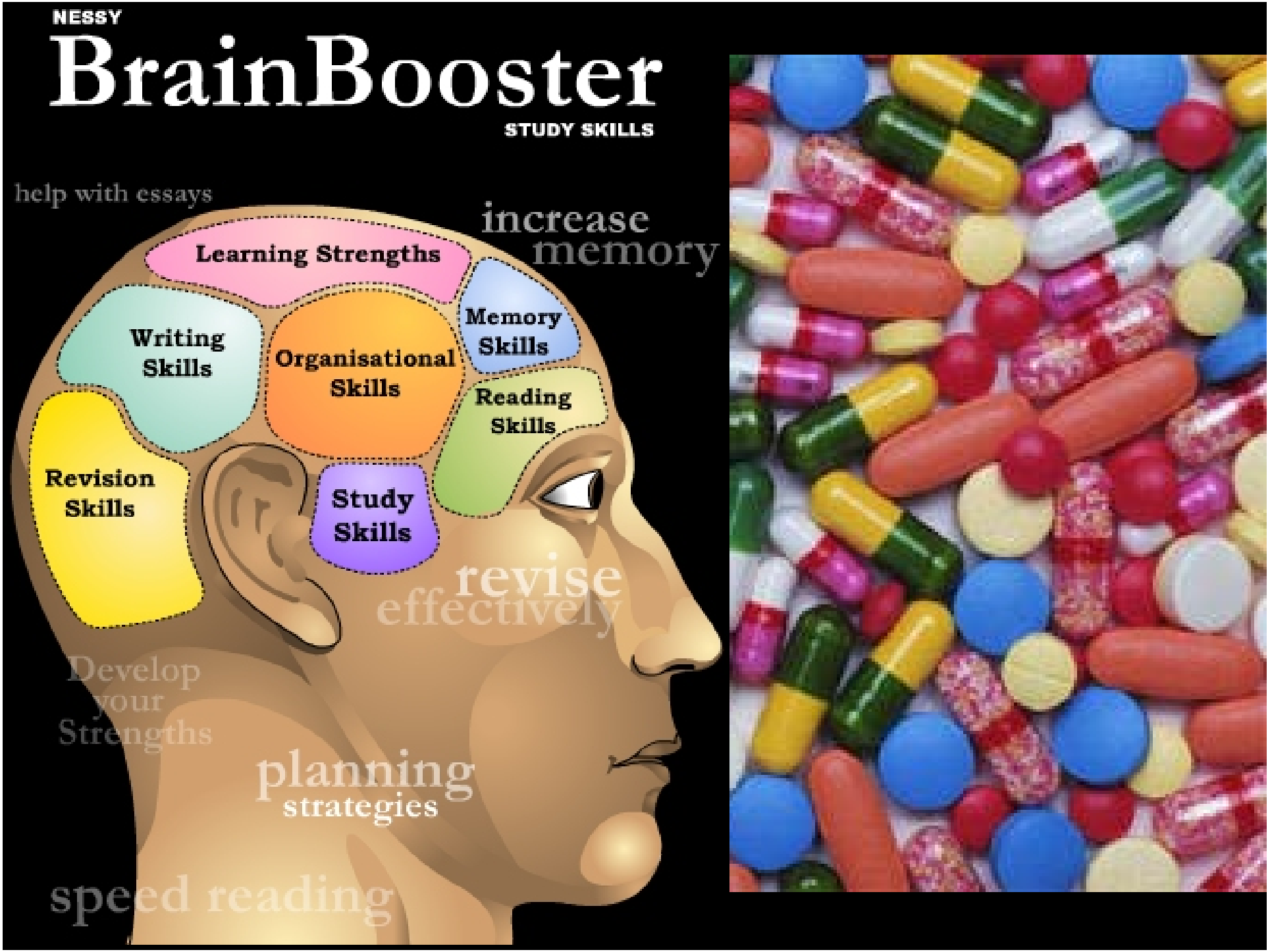



GUINNESS
WORLD RECORDS
CERTIFICATE

NESSY

BrainBooster

STUDY SKILLS



We live in an enhancing society

- Drugs, surgical procedures

If drug and surgical enhancement is OK, why not gene-based enhancement?

- Gene therapy is a reality
- physical (height, strength, etc.) and complex behavioral and social traits (intelligence, personality traits, cognition, mating and sexual behavior, etc.) are partially genetically determined
- We know many of the genes

Sport is ripe for gene-based enhancement

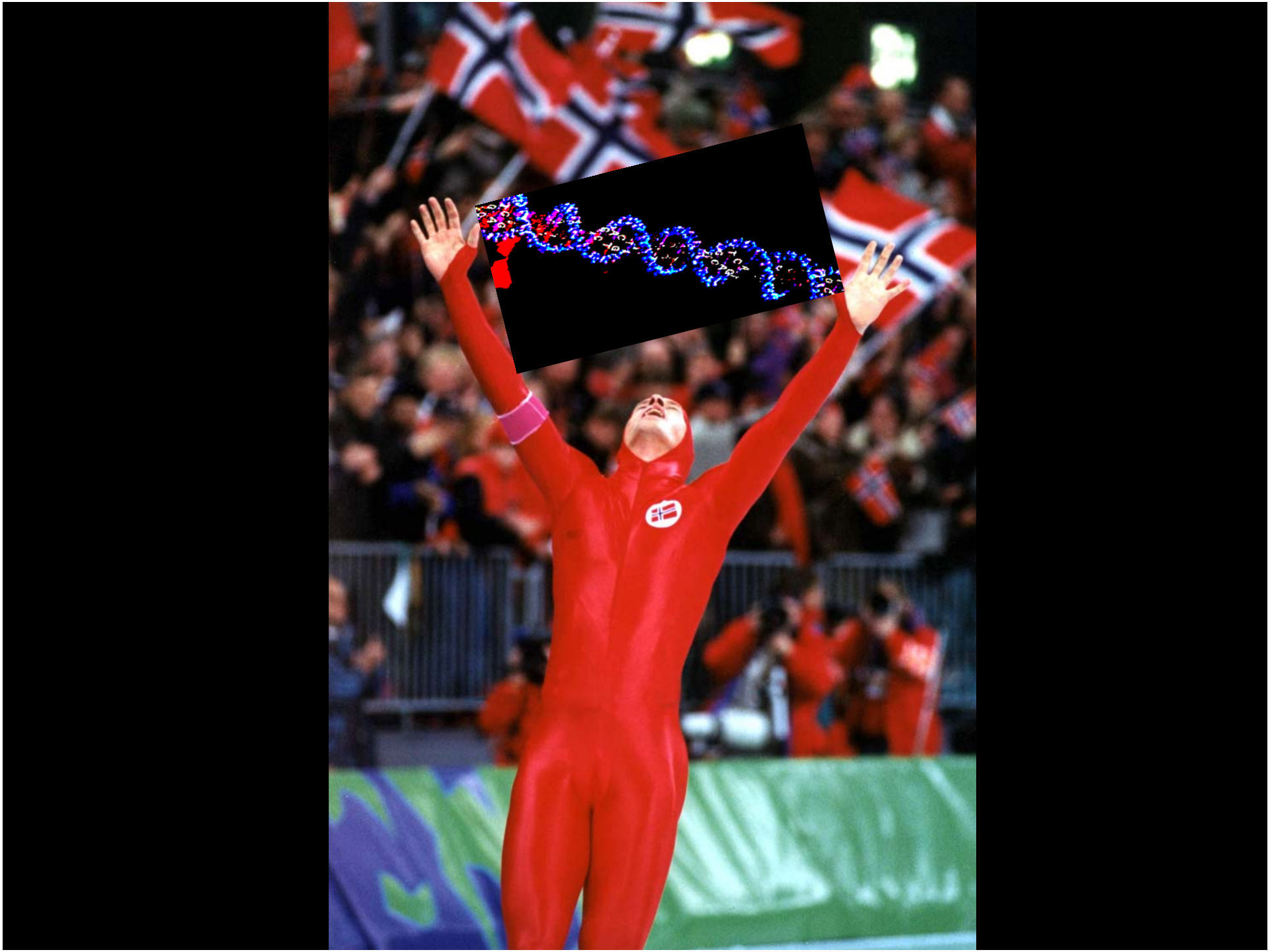
- athletes and handlers are risk-takers
- illicit use of drugs for enhanced performance is common in sport
- tools of gene therapy easily applied to sports
- enormous financial and national pressures at all levels of sport - international elite, national, local


SAN FRANCISCO


SAN FRANCISCO


GIANTS


VIEWIMAGES



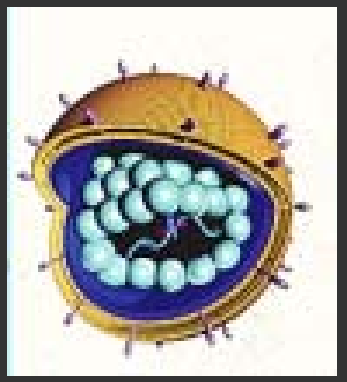
I. Genetic Doping - Origins in Gene Therapy

Which functions might be modified in Sport enhancement?

- Muscle - size, strength, more rapid recovery from injury
- Blood-formation - increase blood flow to exercising tissues
- Production and use of metabolic energy

German Coach Suspected of Genetic Doping (2006)

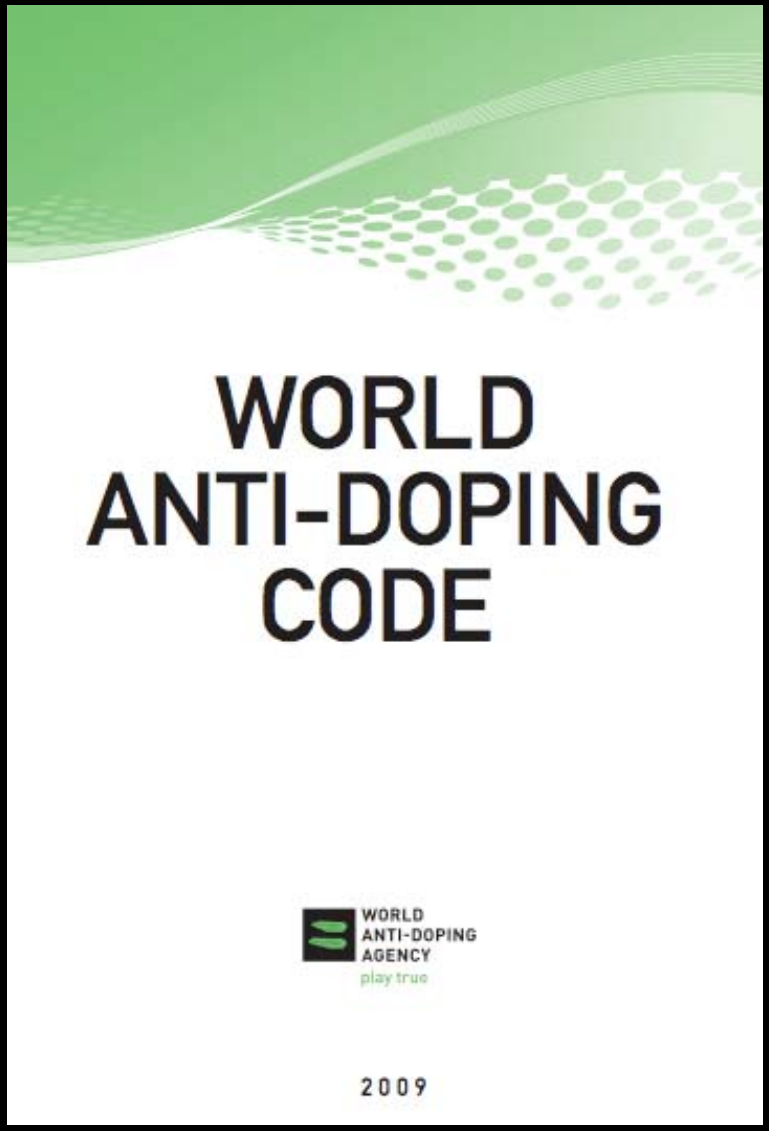
Thomas Springsteen



Repoxygen

Regulated production Of erythropoietin, regulated production of blood

II. Policy revolution – regulate or support doping?



World Anti-Doping Agency (WADA)

USADA

United Nations Educational,
Scientific and Cultural Organization

Declarations Recommendatio
Conventions LEGAL INSTRUMENTS Declar
Recommendations Conventions

Français - Español HOME Print Send

UNESCO Constitution

Y TYPE

International Convention against Doping in Sport 2005

Paris, 19 October 2005

Strong new cottage industry pro-doping

HIGH-TECH HEROES

Enhanced Athletes? It's Only Natural.

By Andy Miah
Sunday, August 3, 2008; Page B01

- To ensure ability of athletes to compete on “level playing field” – everyone free to choose the enhancements that best accentuate their performance. That us what the *natural* athlete *should* look like today”.
- Enhancement includes gene doping…..”*testing is impossible*”
- Encourage drug and surgical modifications
- Invokes a model enhanced athlete – swimmer with surgical enhancement to enlarge webbing in fingers and toes,….leg extension surgery,…

- celebrate rise of new generation of genuinely superhuman athletes, rules of sports are governed by concern for *optimizing excellence*
- Steroids should still be regulated…they are *synthetic drugs that can radically alter the makeup of the body*
- But “tailor-made treatments” (genetic modifications) OK, promise *safer treatments than synthetic substances*
- We want athletes to remain extraordinary – increased use of human enhancement technology is a necessity *– even an obligation*

INTERNATIONAL
Herald Tribune
THE GLOBAL EDITION OF THE NEW YORK TIMES

Health & Science

(Viktor Koen)

John Tierney: Would legal doping level playing field?

By John Tierney

Published: August 12, 2008

nature

International weekly journal of science

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Commentary

Nature **454**, 692-693 (7 August 2008) |
doi:10.1038/454692a; Published online 6 August 2008

The science of doping

Donald A. Berry[1]

ARTICLE LINKS

- Figures and tables

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- "anti-doping authorities have fostered a sporting culture of suspicion, secrecy and fear"

General tenets of pro-doping

- The value of sport is in the spectacle
- Imperfection of testing invalidates the concept and need for anti-doping
- excellence is the feat and the performance - not the achievement
- “extraordinary” is measured by approval of “chicks” and “guys”

Why are these positions so troublesome?

- inconsistent, unrigorous reasoning;
  - steroids should be regulated, but not genes. Steroids are synthetic and can alter makeup of the body. Not true of genes?
  - genes – safer than “synthetic drugs”. What evidence?
  - Testing is impossible - Wrong.
- Pro-doping would optimize “excellence”. Whose excellence – biotechnologist?

Beijing Paralympics 20

The fallacy

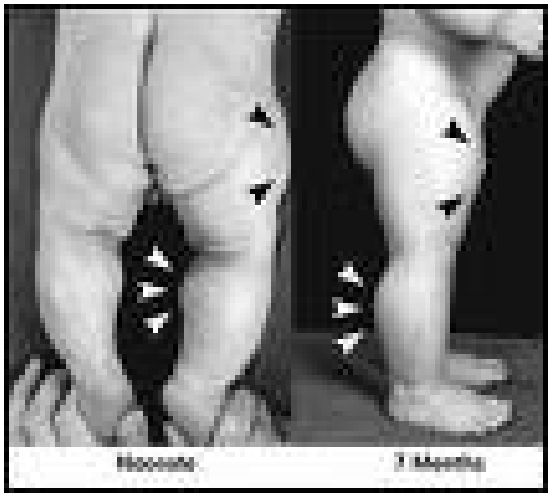
- Athletic ability is largely genetic

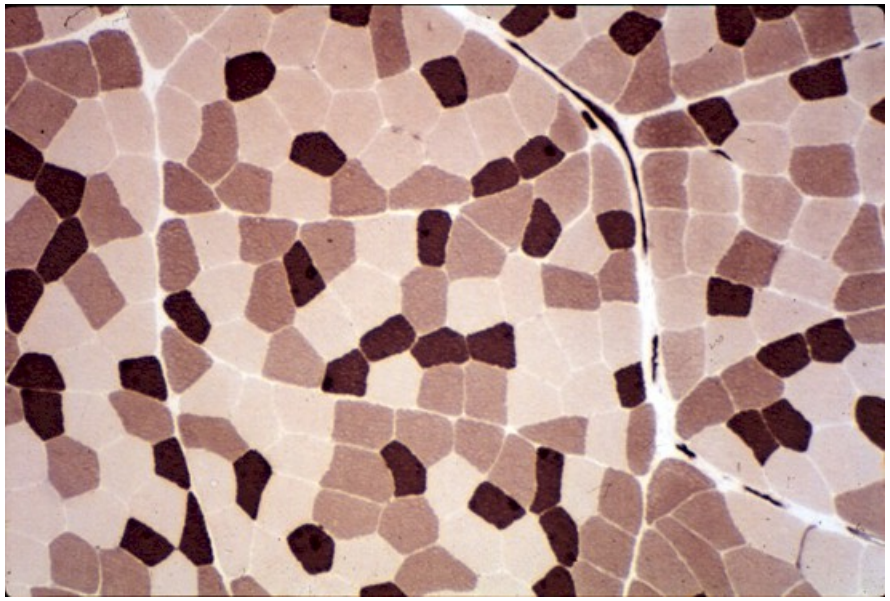
Are there genes that determine athletic ability

- of course
- Growth factors - IGF-1, HGH
- ACTN3 - determines muscle twitch fiber type - screening program by Australian company
- PEPCK-C - phosphenolpyruvate carboxykinase
- PPARd - peroxisome proliferator-activated receptors - metabolic regulator

Genes play major role in our physical structure - growth factors

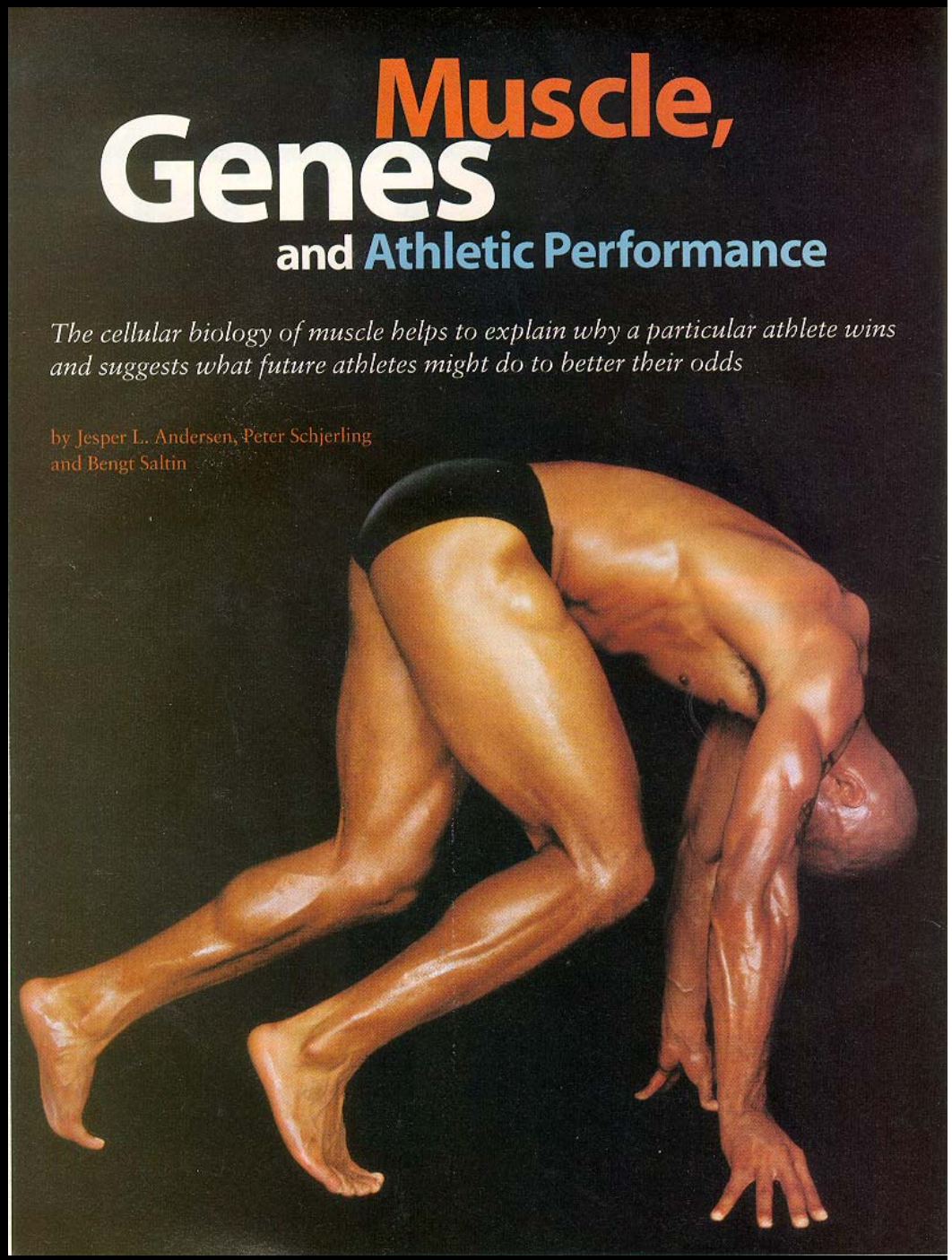
Genes for specific athletic capability - muscle growth and function



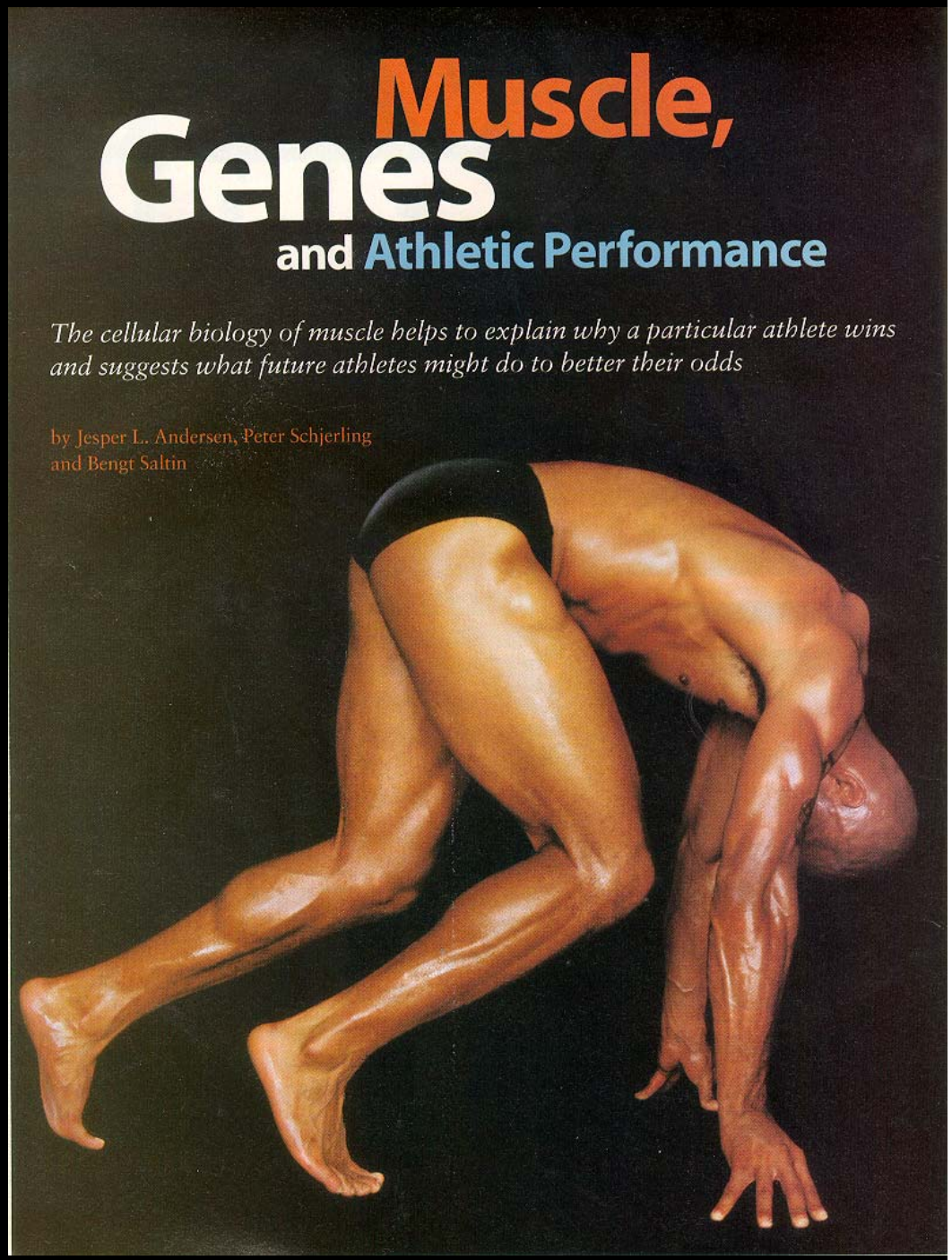


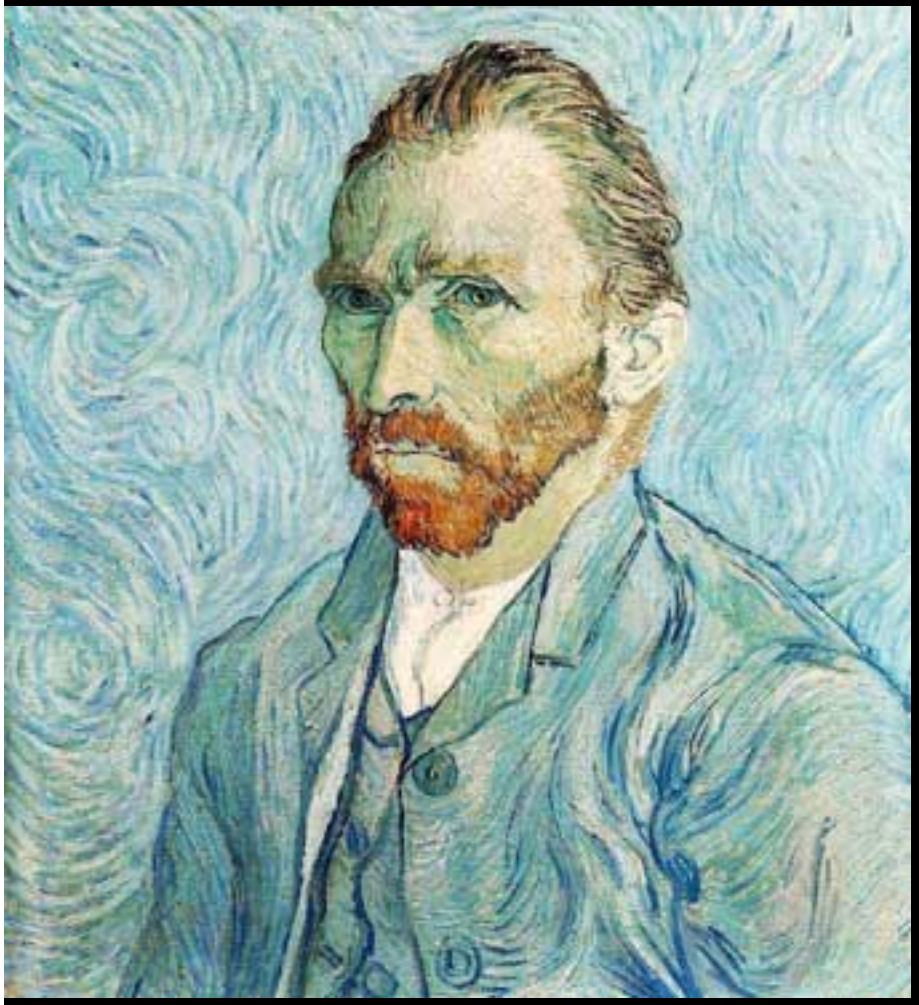
There is no single “athletic” gene

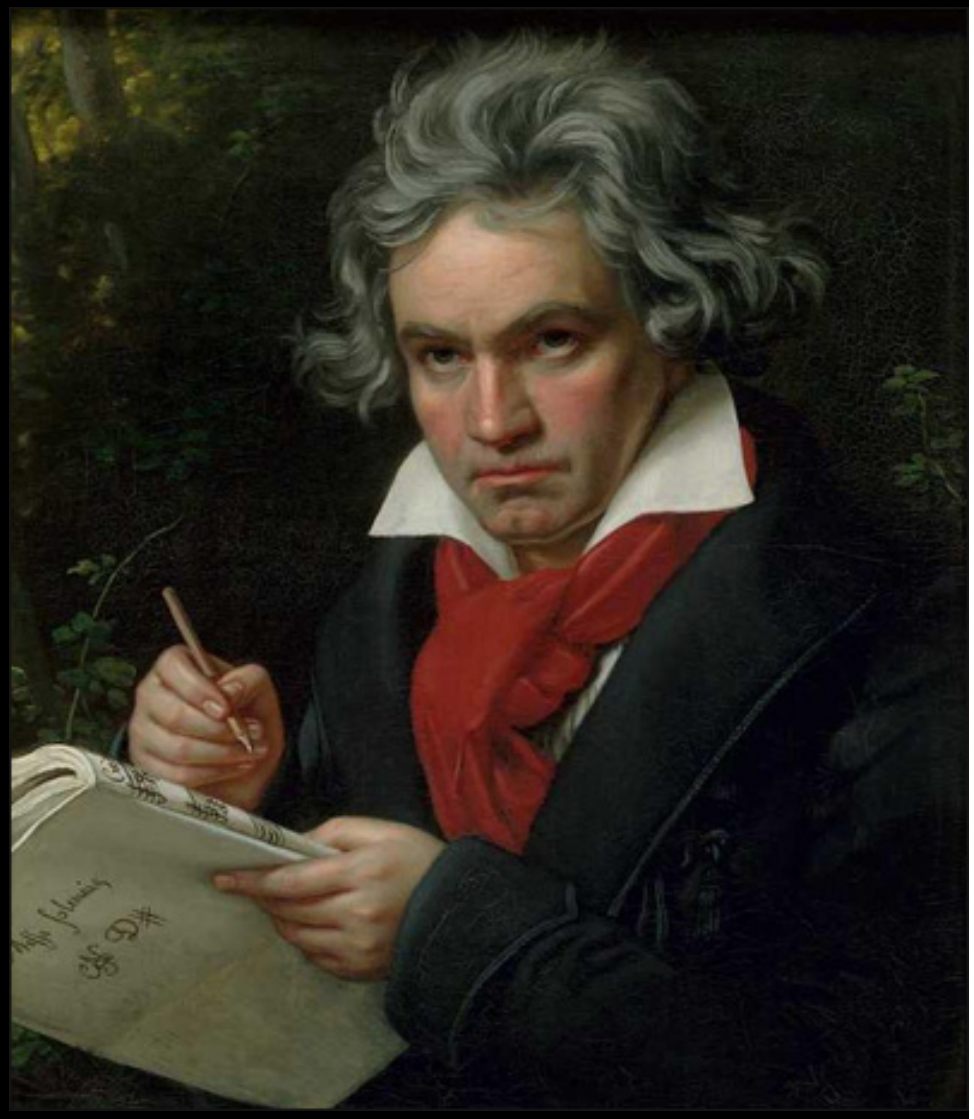
genetic traits



environment
(opportunities, training, etc.)

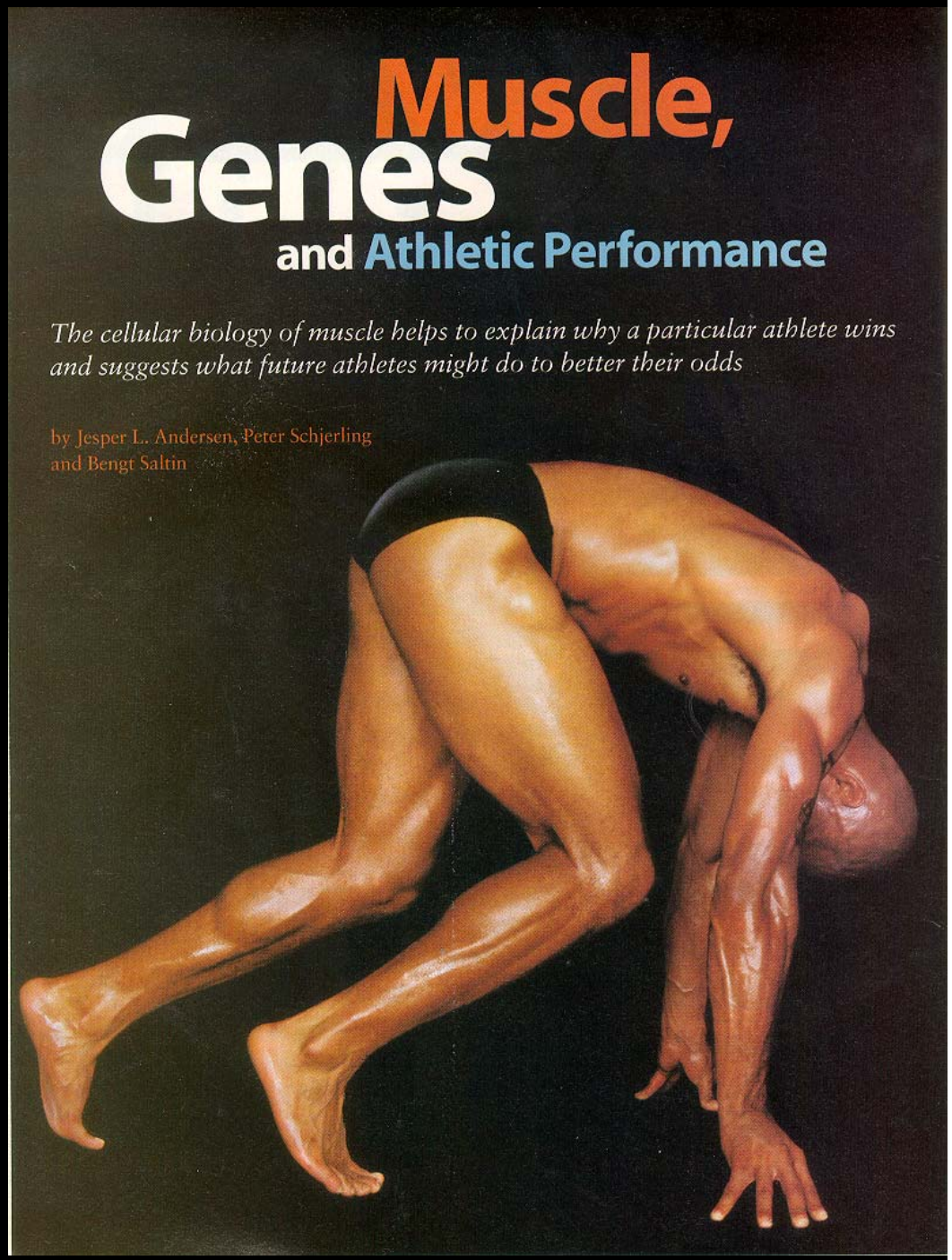






genetic traits

environment (opportunities, training, etc.)



These traits can be altered

- by environmental manipulations
- by genetic methods?

There is no single “athletic” gene

genetic technologies

Genetic Technologies Limited

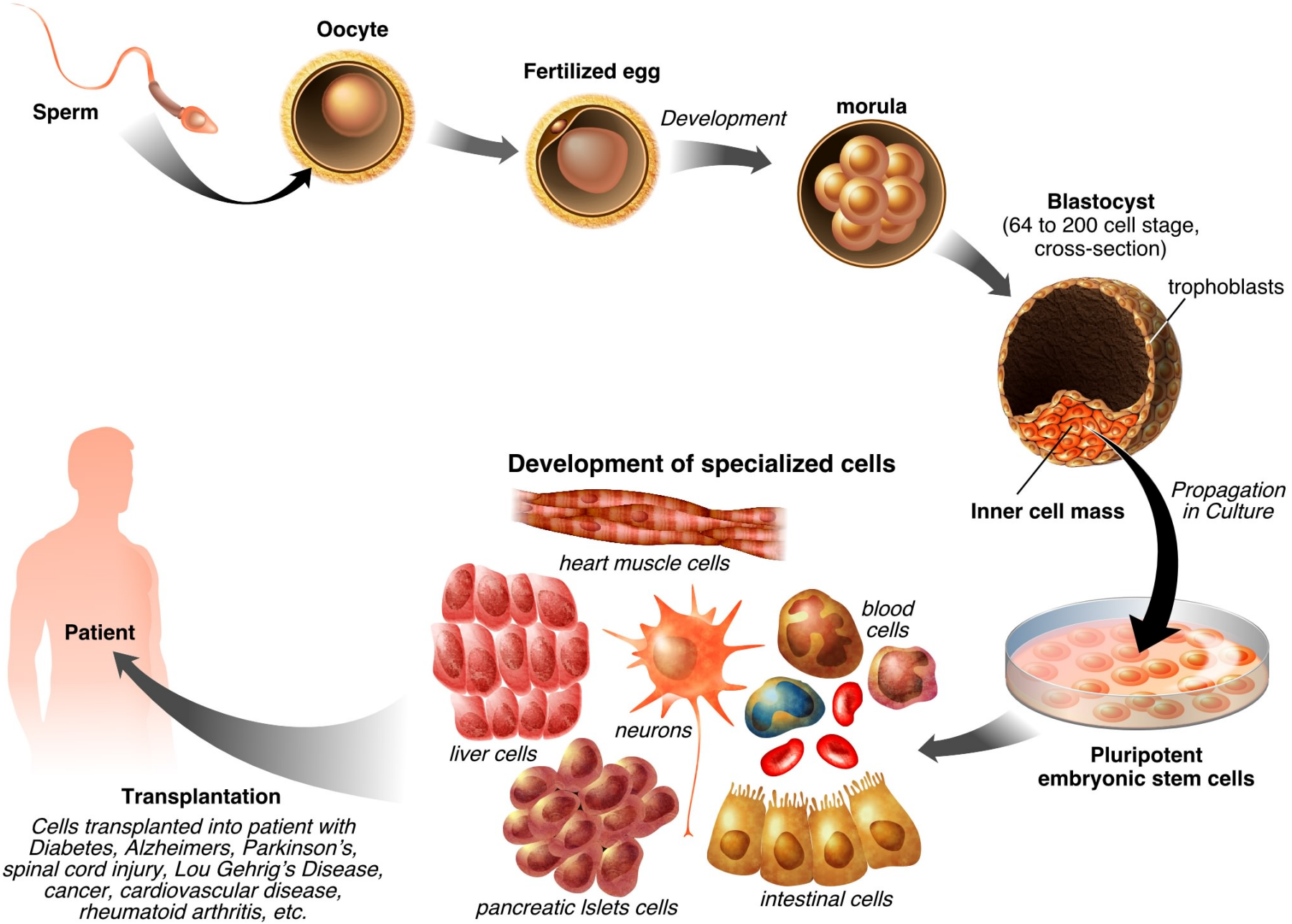
Delivering the benefits of the genetic revolution

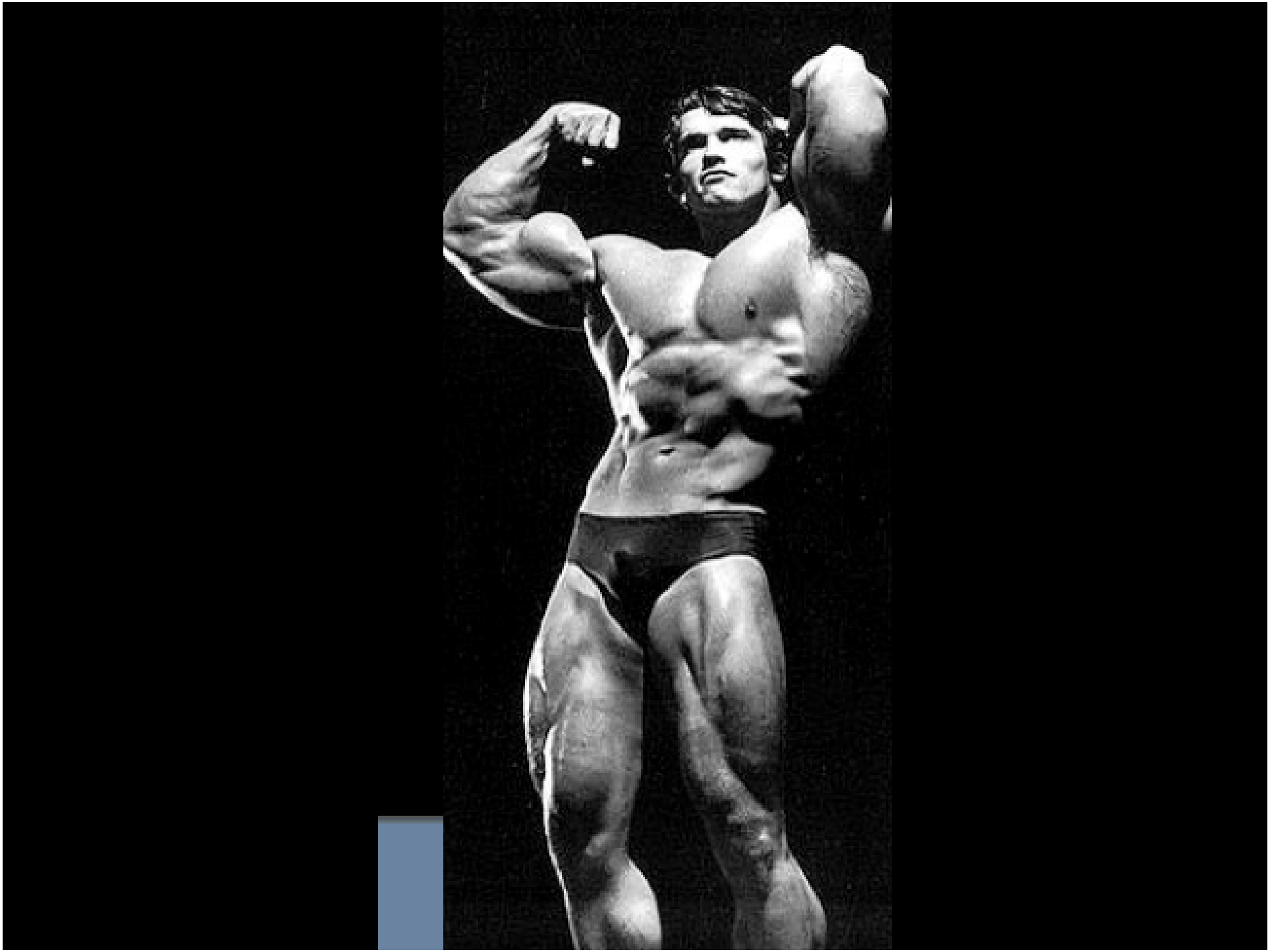
Genetic Technologies (ASX: GTG, NASDAQ Global Market: GENE) specialises in licensing, genetic testing and research. GTG's exclusive access to a wide range of genetic tests enables it to expand its testing services throughout the Asia-Pacific region. GTG's pipeline of innovative research projects will potentially add considerable value to its licensing and genetic testing businesses.

People Genetic testing for disease susceptibility, parentage, individual identity, forensics and sports performance (ACTN3).

Search

Stem Cell Therapy





Birth of Eugenics – mid-late 19th century England

- Francis Galton – cousin of Darwin.
- talent is hereditary (*Hereditary Genius – 1869*)
- human society can be improved
- 1883 - coined phrase “eugenics” – “good origin”
- social ills can and should can be prevented by selective breeding

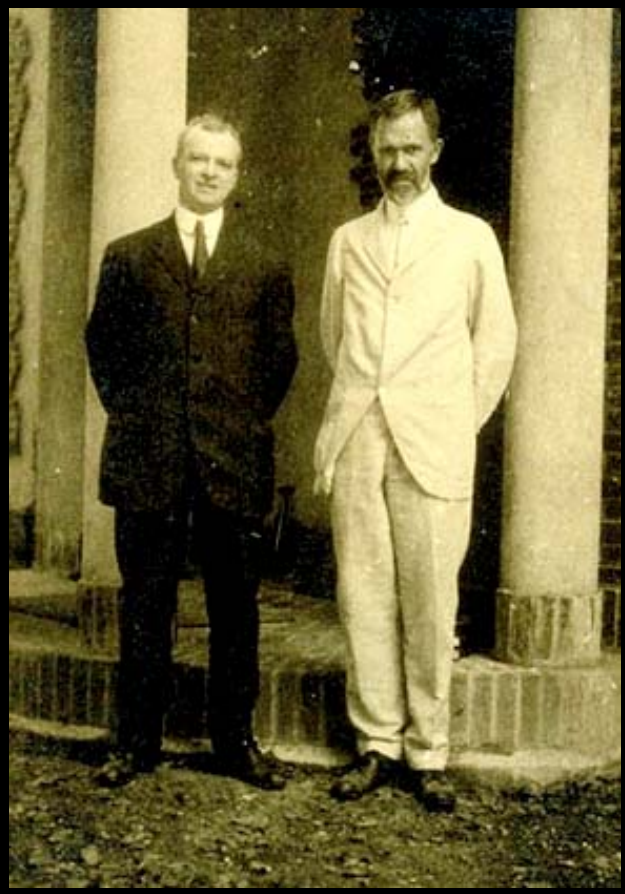
Cold Spring Harbor
Genetics Record Office
1905

Charles Davenport – lost son to polio

Harry Laughlin - epilepsy

Cold Spring Harbor Genetics - Record Office 1905

Harry Laughlin - assistant to Davenport. Compulsory sterilization and restrictive immigration policies to ensure racial purity. Nazi *Law for the Prevention of Hereditarily Diseased Offspring* in 1933. Honorary degree Heidelberg University in 1936 for his many "contributions to racial cleansing"

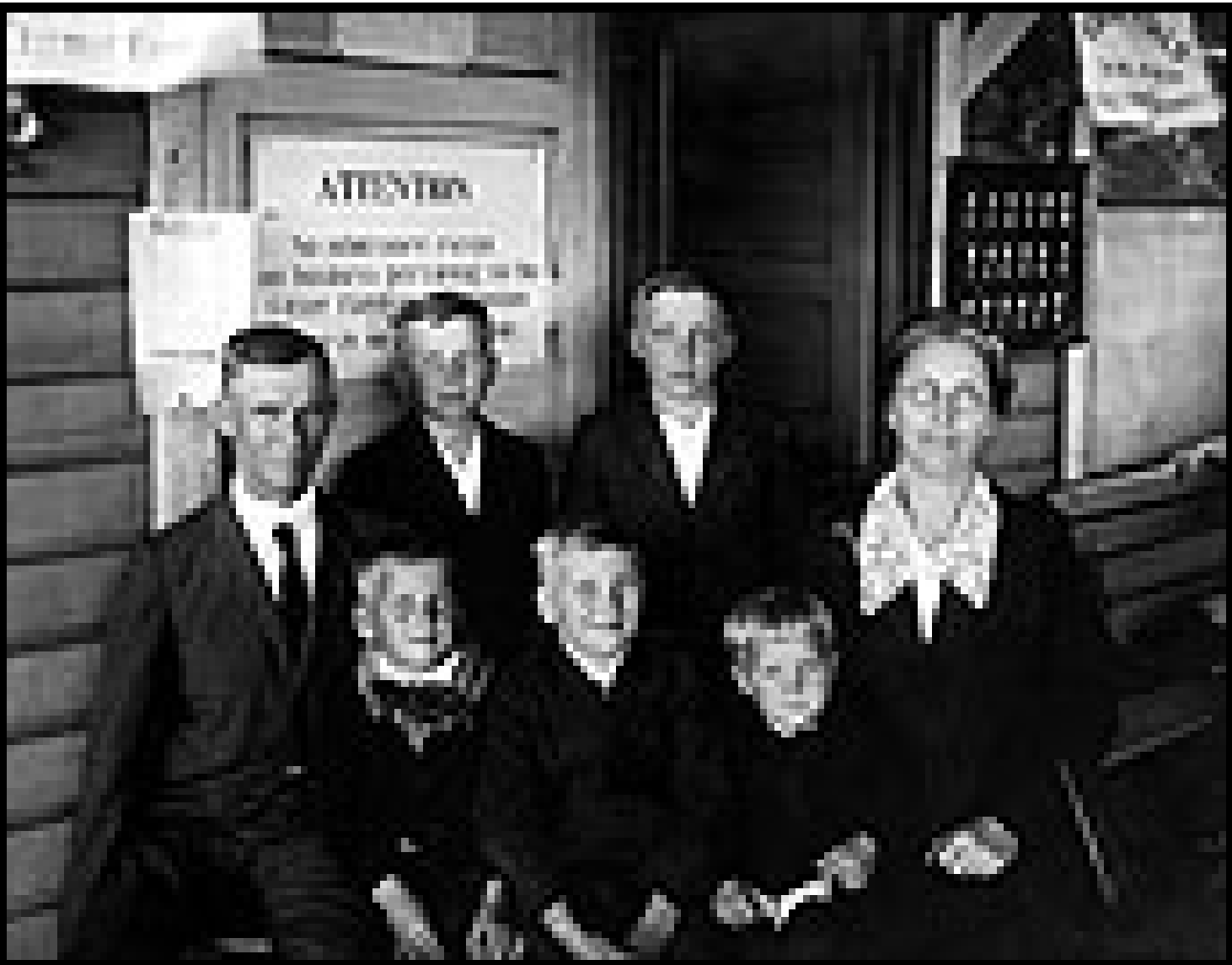


Charles Davenport - director. Poverty, wantonness, epilepsy, hereditary disease are biological weaknesses, can be eliminated by selective breeding

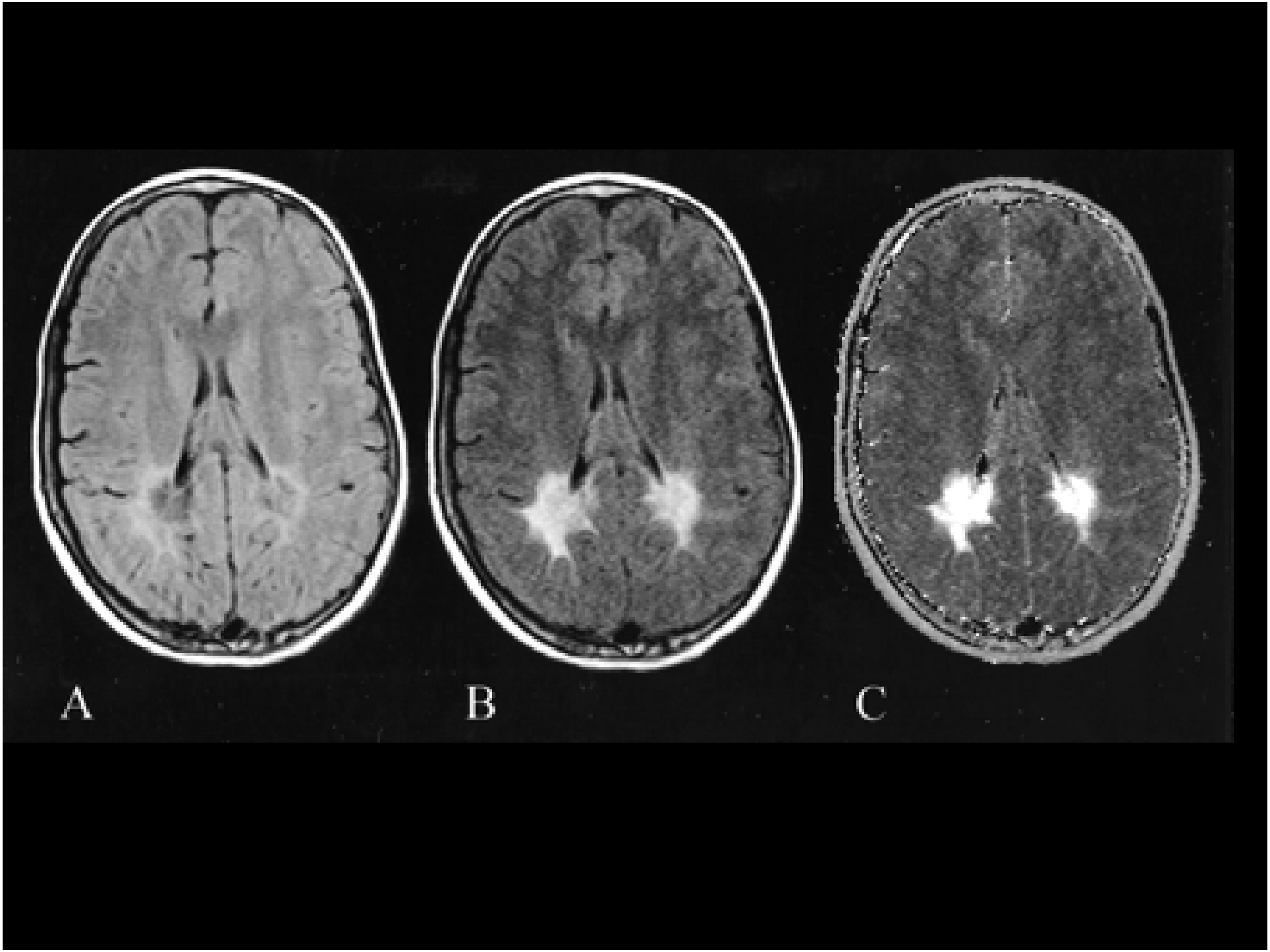
The Davenport Family, c. 1916

"We have seen more than once that the public welfare may call upon the best citizens for their lives. It would be strange if it could not call upon those who already sap the strength of the State for these lesser sacrifices, often not felt to be such by those concerned, in order to prevent our being swamped with incompetence. It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes. Three generations of imbeciles are enough."

- Supreme Court Justice Oliver Wendell Holmes, Jr. in the majority decision *Buck v. Bell*, 1927



Honorable mention – large family class.
Kansas Fair, 1923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