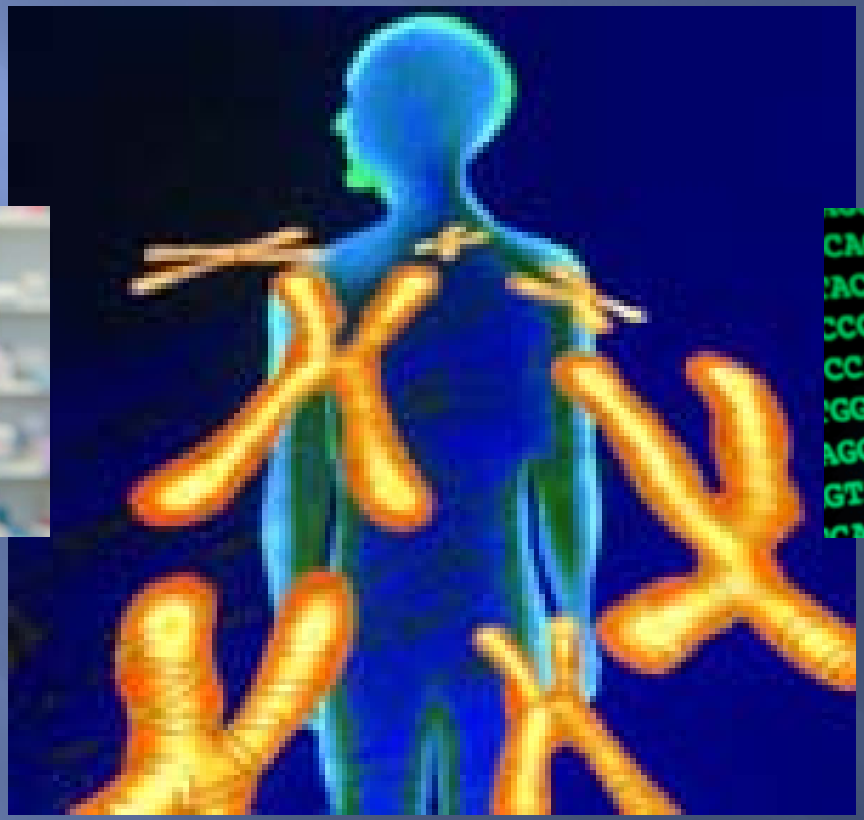
Pharmacogenetics

A Primer on an Emerging Discipline and Way of Thinking



Chuck Biddle CRNA, PhD
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"IF IT WERE NOT FOR THE GREAT VARIABILITY AMONG INDIVIDUALS, TAKING CARE OF PATIENTS MIGHT AS WELL BE A SCIENCE AND NOT AN ART"

– SIR WILLIAM OSLER 1892

ORIGINAL INVESTIGATION

High Rates of Adverse Drug Events in a Highly Computerized Hospital

ARCHIVES EXPRESS

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Background: Numerous studies have shown that specific computerized interventions may reduce medication errors, but few have examined adverse drug events (ADEs) across all stages of the computerized medication process. We describe the frequency and type of inpatient ADEs that occurred following the adoption of multiple computerized medication ordering and administration systems, including computerized physician order entry (CPOE).

Methods: Using explicit standardized criteria, pharmacists classified inpatient ADEs from prospective daily reviews of electronic medical records from a random sample of all admissions during a 20-week period at a Veterans Administration hospital. We analyzed ADEs that necessitated a changed treatment plan.

Results: Among 937 hospital admissions, 483 clinically significant inpatient ADEs were identified, accounting for 52 ADEs per 100 admissions and an incidence density of 70 ADEs per 1000 patient-days. One quarter of the hospitalizations had at least 1 ADE. Of all ADEs, 9% resulted in serious harm, 22% in additional monitoring and interventions, 32% in interventions alone, and 11% in monitoring alone; 27% should have resulted in additional interventions or monitoring. Medication errors contributed to 27% of these ADEs. Errors associated with ADEs occurred in the following stages: 61% ordering, 29% monitoring, 13% administration, 1% dispensing, and 0% transcription. The medical record reflected recognition of 76% of the ADEs.

Conclusions: High rates of ADEs may continue to occur after implementation of CPOE and related computerized medication systems that lack decision support for drug selection, dosing, and monitoring.

Arch Intern Med. 2005;165:1111-1116

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Financial Disclosure: None.

MULTIPLE BROAD-BASED studies during the past 15 years have demonstrated that adverse drug events (ADEs) account for up to 41%[1] of all hospital admissions and more than $2 billion annually in inpatient costs.[2-4] Several of these studies have also estimated that as many as a quarter of inpatient ADEs may be preventable through interventions such as computerized physician order entry (CPOE) and related systems.[5-7] On the basis of these projections and the proven success of these systems in identifying ADEs and reducing medication errors,[8-11] computerized medication processes have been widely promoted as essential to preventing actual ADEs.[9,12,13]

Recently, some researchers have questioned the extent to which currently available CPOE and related systems are preventing ADEs.[14-16] There are concerns that features of commercial CPOE products vary widely and that few can match the sophistication of custom systems developed at institutions that have successfully reduced targeted ADEs.[13,17-21] Moreover, broad-based surveys of ADEs in institutions that have implemented multiple computerized medication systems have not been published; it is unclear how these interventions together have affected the occurrence of ADEs linked to problems across stages of medication processing (ie, ordering, transcription, dispensing, administration, and monitoring).[3]

The Veterans Administration (VA) Healthcare System, one of the largest integrated delivery systems in the country, is a leader in patient safety and has actively sought to reduce medication errors using multiple computerized interventions such as CPOE,[22-25] bar code–controlled medication delivery,[8,20,26] a complete electronic medical record,[1,26-31] automated drug-drug interaction checking,[32-35] and computerized allergy tracking and alerting.[36-38] The White House has

Arch Int Med 2005;165:1111-6

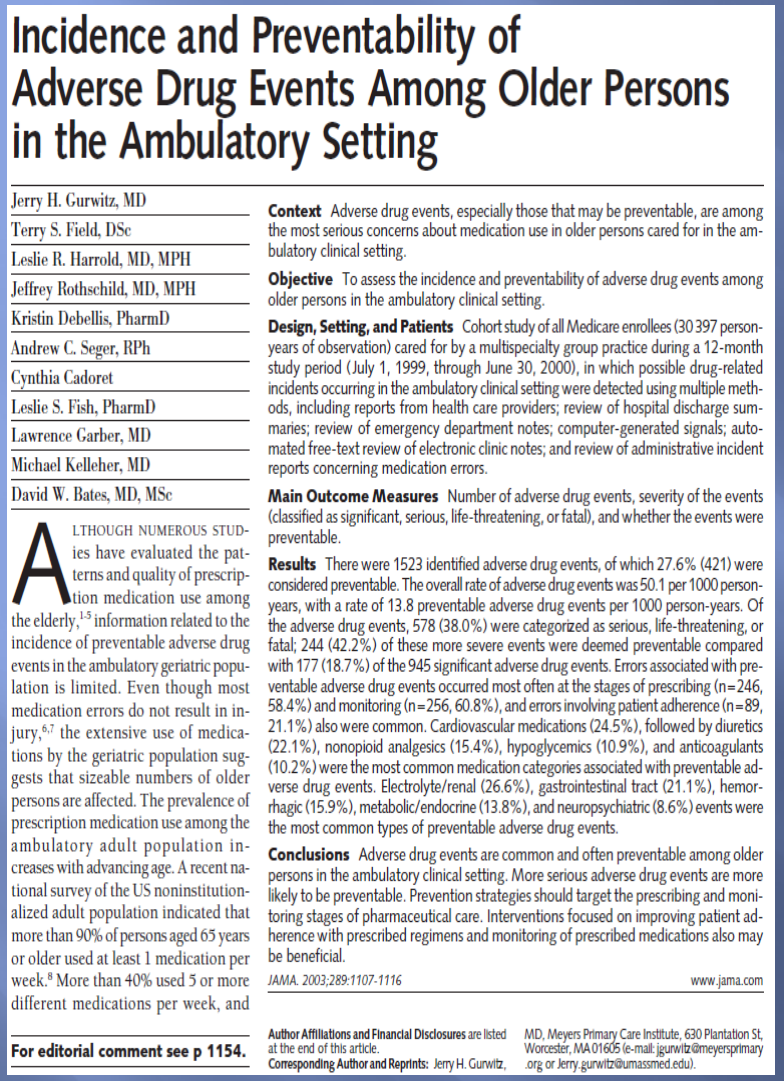
ADEs known to account for up to 41% of hospital admissions

Study from LDS Hospital (UT) Stat-of-art electronic Rx systems

Here investigators found:

6.6 serious & 0.9 fatal ADEs per 1000 patient days

110 bed hospital = 40 deaths / yr



Incidence and Preventability of Adverse Drug Events Among Older Persons in the Ambulatory Setting

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Context Adverse drug events, especially those that may be preventable, are among the most serious concerns about medication use in older persons cared for in the ambulatory clinical setting.

Objective To assess the incidence and preventability of adverse drug events among older persons in the ambulatory clinical setting.

Design, Setting, and Patients Cohort study of all Medicare enrollees (30 397 person-years of observation) cared for by a multispecialty group practice during a 12-month study period (July 1, 1999, through June 30, 2000), in which possible drug-related incidents occurring in the ambulatory clinical setting were detected using multiple methods, including reports from health care providers; review of hospital discharge summaries; review of emergency department notes; computer-generated signals; automated free-text review of electronic clinic notes; and review of administrative incident reports concerning medication errors.

Main Outcome Measures Number of adverse drug events, severity of the events (classified as significant, serious, life-threatening, or fatal), and whether the events were preventable.

Results There were 1523 identified adverse drug events, of which 27.6% (421) were considered preventable. The overall rate of adverse drug events was 50.1 per 1000 person-years, with a rate of 13.8 preventable adverse drug events per 1000 person-years. Of the adverse drug events, 578 (38.0%) were categorized as serious, life-threatening, or fatal; 244 (42.2%) of these more severe events were deemed preventable compared with 177 (18.7%) of the 945 significant adverse drug events. Errors associated with preventable adverse drug events occurred most often at the stages of prescribing (n=246, 58.4%) and monitoring (n=256, 60.8%), and errors involving patient adherence (n=89, 21.1%) also were common. Cardiovascular medications (24.5%), followed by diuretics (22.1%), nonopioid analgesics (15.4%), hypoglycemics (10.9%), and anticoagulants (10.2%) were the most common medication categories associated with preventable adverse drug events. Electrolyte/renal (26.6%), gastrointestinal tract (21.1%), hemorrhagic (15.9%), metabolic/endocrine (13.8%), and neuropsychiatric (8.6%) events were the most common types of preventable adverse drug events.

Conclusions Adverse drug events are common and often preventable among older persons in the ambulatory clinical setting. More serious adverse drug events are more likely to be preventable. Prevention strategies should target the prescribing and monitoring stages of pharmaceutical care. Interventions focused on improving patient adherence with prescribed regimens and monitoring of prescribed medications also may be beneficial.

JAMA. 2003;289:1107-1116 www.jama.com

ALTHOUGH NUMEROUS STUDIES have evaluated the patterns and quality of prescription medication use among the elderly,[1-5] information related to the incidence of preventable adverse drug events in the ambulatory geriatric population is limited. Even though most medication errors do not result in injury,[6,7] the extensive use of medications by the geriatric population suggests that sizeable numbers of older persons are affected. The prevalence of prescription medication use among the ambulatory adult population increases with advancing age. A recent national survey of the US noninstitutionalized adult population indicated that more than 90% of persons aged 65 years or older used at least 1 medication per week.[8] More than 40% used 5 or more different medications per week, and

For editorial comment see p 1154.

Author Affiliations and Financial Disclosures are listed at the end of this article.
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JAMA 2003;289:1107-16

What we know:

~ 2 million ADEs annually
~ 200,000 life threatening or fatal

Estimates are likely very conservative (underreporting)

How to improve things?

- Curb use—seek alternatives
- Stop Rx early if ADE
- Improve compliance
- Careful, ongoing evaluation
- Education (provider + patient)
- Improve reporting
- *Pharmacogenetics research*

The American Journal of Medicine (2005) 118, 251–258

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CLINICAL RESEARCH STUDY

The incidence of adverse drug events in two large academic long-term care facilities

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KEYWORDS:
Adverse drug events;
Nursing homes;
Medication errors;
Patient safety

PURPOSE: To assess the incidence of and risk factors for adverse drug events in the long-term care setting.

METHODS: We performed a cohort study of all long-stay residents of two academic long-term care facilities over a period of up to 9 months during 2000 to 2001. We assessed the number of adverse drug events, the severity of events (classified as less serious, serious, life threatening, or fatal), and whether the events were preventable. A case-control study was nested within the prospective study to identify resident-level risk factors for the occurrence of adverse drug events.

RESULTS: There were 815 adverse drug events, of which 42% were judged preventable. The overall rate of adverse drug events was 9.8 per 100 resident-months, with a rate of 4.1 preventable adverse drug events per 100 resident-months. Errors associated with preventable events occurred most often at the stages of ordering and monitoring. Residents taking medications in several drug categories were at increased risk of a preventable adverse event. In multivariate analyses, the adjusted odds ratio was 3.4 (95% confidence interval [CI]: 2.0 to 5.9) for those taking antipsychotic agents, 2.8 (95% CI: 1.6 to 4.7) for those taking anticoagulants, 2.2 (95% CI: 1.2 to 4.0) for those taking diuretics, and 2.0 (95% CI: 1.1 to 3.7) for those taking antiepileptics.

CONCLUSION: Our findings reinforce the need for a special focus on the ordering and monitoring stages of pharmaceutical care for preventing adverse drug events in the long-term care setting. Patients taking antipsychotic agents, anticoagulants, diuretics, and antiepileptics are at increased risk.

Am J Med 2005;118:251-8

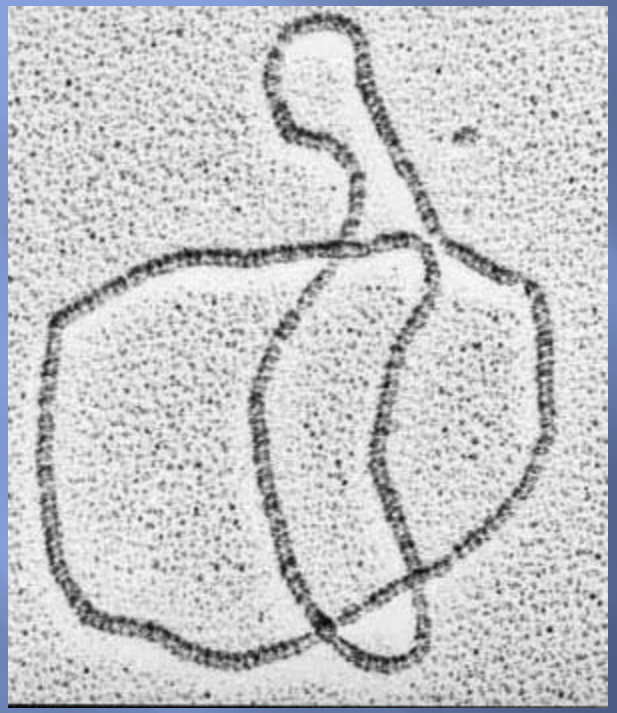
Table 3 Frequency of adverse drug events by drug type*

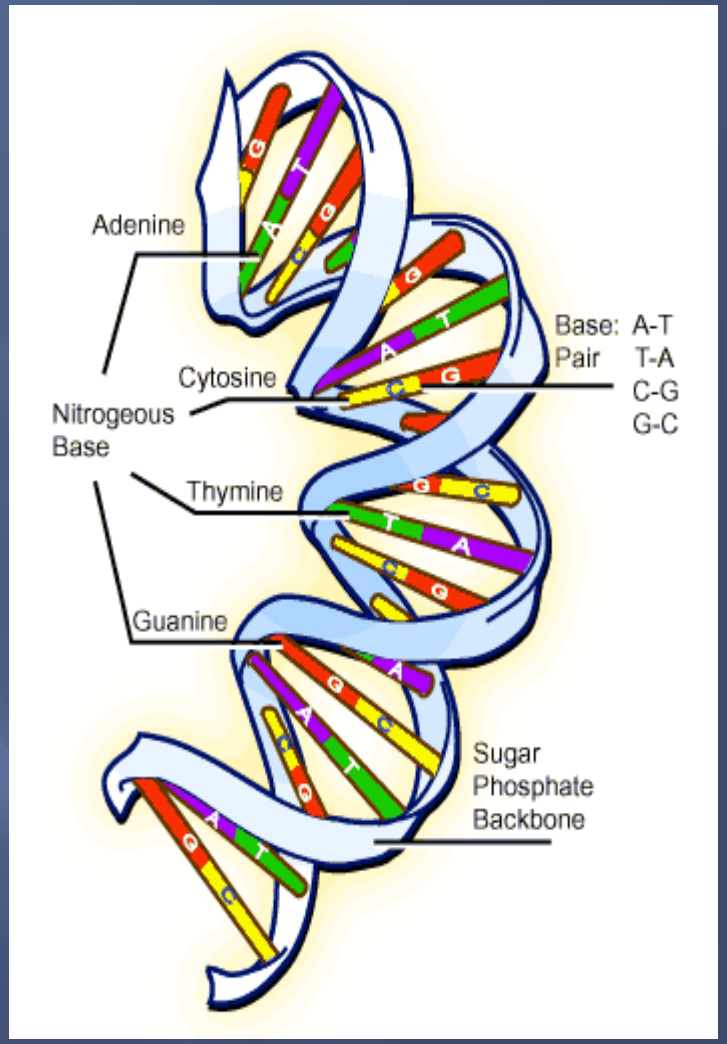
Drug Class	Total (n = 815) Number (%)	Preventable (n = 338) Number (%)
Warfarin	121 (15)	42 (12)
Atypical antipsychotic agents†	92 (11)	42 (12)
Loop diuretics	69 (8)	33 (10)
Opioids	51 (6)	26 (8)
Antiplatelets	46 (6)	23 (7)
ACE inhibitors	45 (6)	27 (8)
Antidepressants (non-SSRI, nontricyclic)‡	43 (5)	25 (7)
Laxatives	43 (5)	16 (5)
Benzodiazepines (intermediate acting)§	39 (5)	30 (9)
Insulins	37 (5)	18 (5)
Quinolones	27 (3)	2 (1)
Clindamycin	23 (3)	2 (1)
Valproic acid	22 (3)	11 (3)
SSRIs	21 (3)	10 (3)
Potassium-sparing diuretics	20 (2)	9 (3)
COX-2 inhibitors	19 (2)	11 (3)
Beta-blockers	18 (2)	7 (2)
Trimethoprim-sulfamethoxazole	17 (2)	6 (2)
Typical antipsychotic agents		
Phenytoin		
Thyroid		
Nitrates		
Tricyclic antidepressants		
Penicillins		
Cephalosporins		
Thiazide diuretics		
Benzodiazepines (long-acting)		
Heparin		
Dopamine agonists		
Bladder medications#		
Gabapentin		
Digoxin		
Benzodiazepines (short-acting)		
Antihistamines		
Glyburide		
NSAIDs (traditional)		

Table 1 Severity and effects of adverse drug events

	Total (n = 815) Number (%)	Preventable (n = 338) Number (%)
Category of severity		
Fatal	4 (<1)	3 (1)
Life threatening	33 (4)	24 (7)
Serious	188 (23)	110 (32)
Less serious	590 (72)	201 (60)
Effects of adverse drug events		
Only laboratory abnormality	68 (8)	27 (8)
≤1 day of symptoms	148 (18)	46 (14)
>1 day of symptoms	590 (72)	259 (76)
Nonpermanent disability	3 (<1)	2 (1)
Permanent disability	2 (<1)	1 (<1)
Death	4 (<1)	3 (1)

Genetics “101”



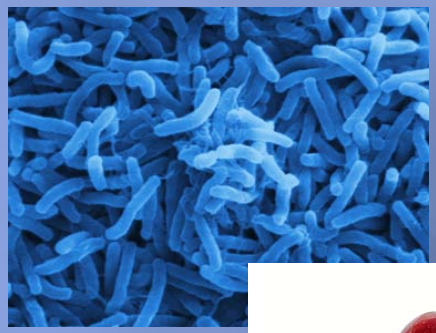


DNA:

- **4 types of nucleotides**
- **Each has a phosphate group, a sugar and a combination of purine or pyrimidine bases:**

Adenine Guanine Thymine Cytosine

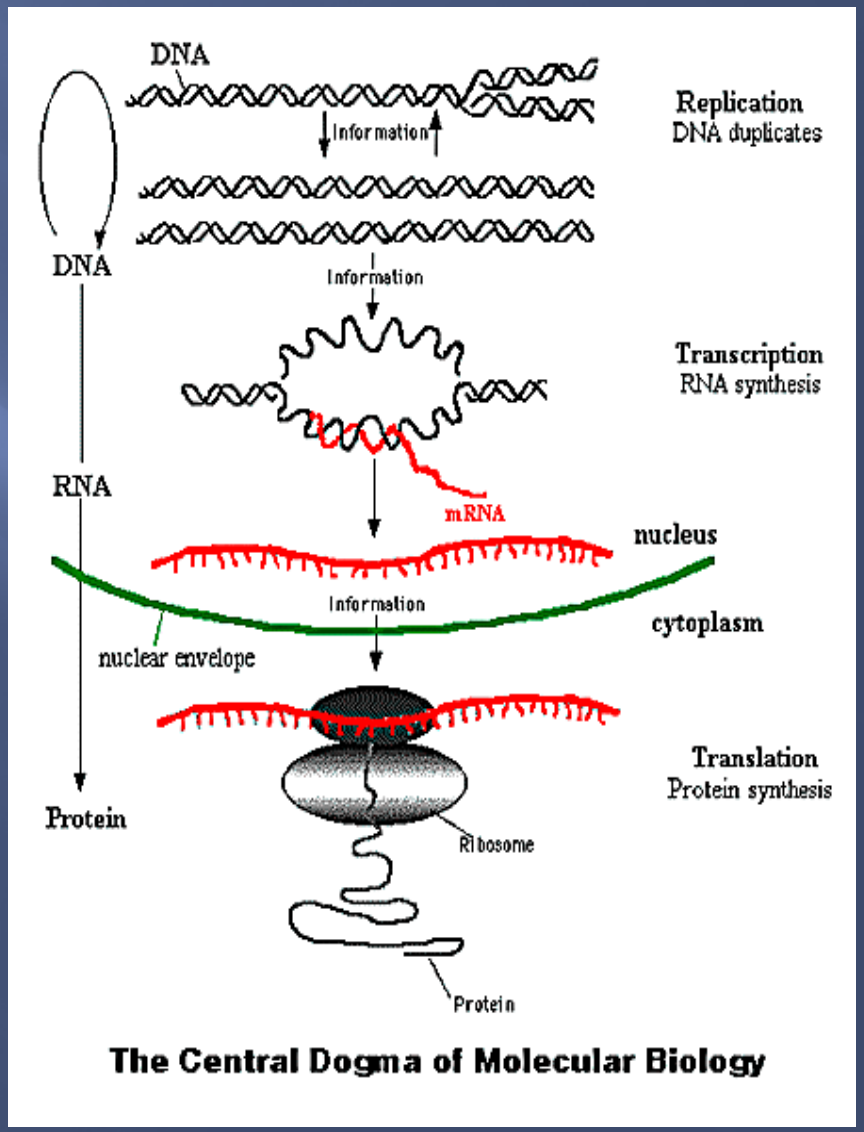
- Bacteria, apples , porcupines, people have DNA
- All of the DNA of an organism = genome



- Human genome = ~ 3 billion pairs of nucleotides
- We share same sequence on ~99.9% of the genome
- Still leaves millions of differing locations

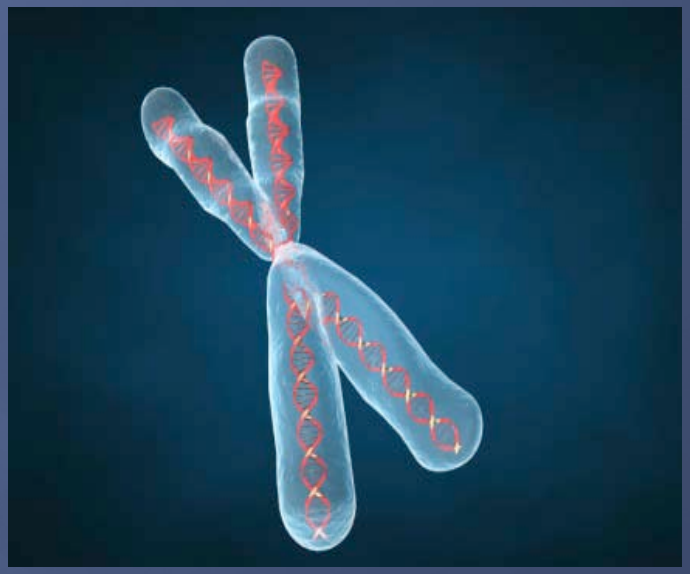
Genetics “101”

- DNA serves as a template for mRNA transcription
- Mature mRNA ‘travels’ to cytoplasm, undergoes translation into protein



The Central Dogma of Molecular Biology

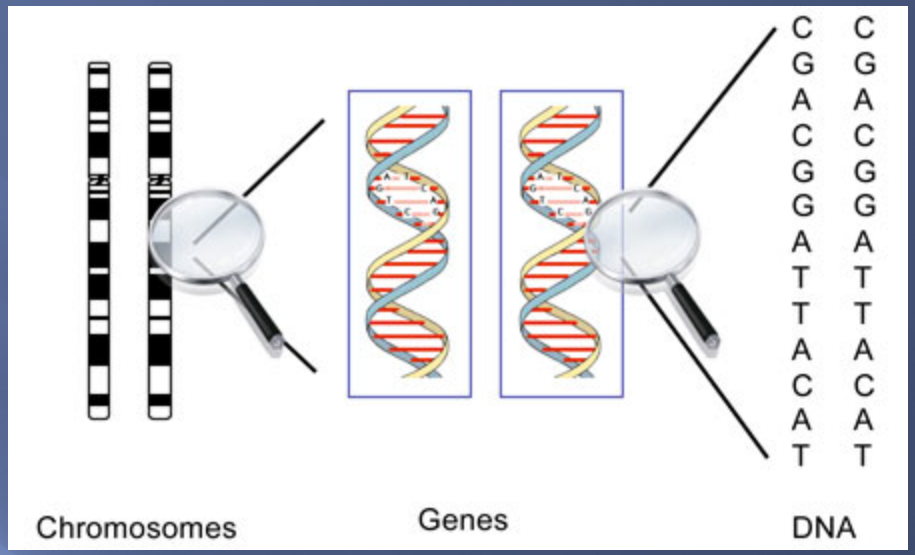
Genetics "101", cont'…



- Gene → the unit of inheritance
- Gene → carries instructions to make proteins
- Carried as segments on chromosomes
- We have 2 copies of each gene (1 from each parent)
- Each of us has 20,000 – 25,000 genes
- Sequence >99% identical in all humans

- Tiny variation in our genes makes each of us unique

Genes



- **Shortest: a few hundred base pairs long**
- **Longest: Duchenne MD gene > 2 million base pairs**

- **Our specific DNA sequence harbors clues to our susceptibility to disease and response to drugs**

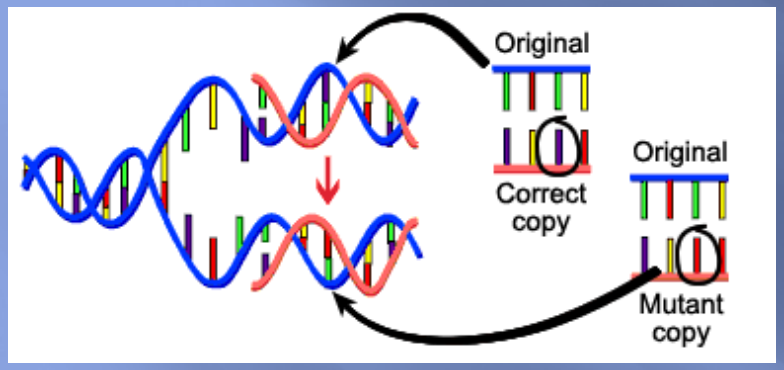
Genetics "101", cont'…
Mutation *vs* Polymorphism

- **Variably defined……**

- **Mutation**
  - Induced from outside the cell by an exogenous factor
  - Heritable, not necessarily harmful
  - Occurs in < 1% of the population

- **Polymorphism**
  - Induced from within the cell
  - Evolution → cell changes to conform / to adapt
  - Heritable, not necessarily harmful
  - Occurs in at least 1% of the population

Mutations/polymorphisms



altered DNA segments

-Most common variation is the *point mutation*

+ > 13 million identified

+ Also *insertions, deletions, etc*

-Often silent, may be significant

-Directly alter AA-based proteins

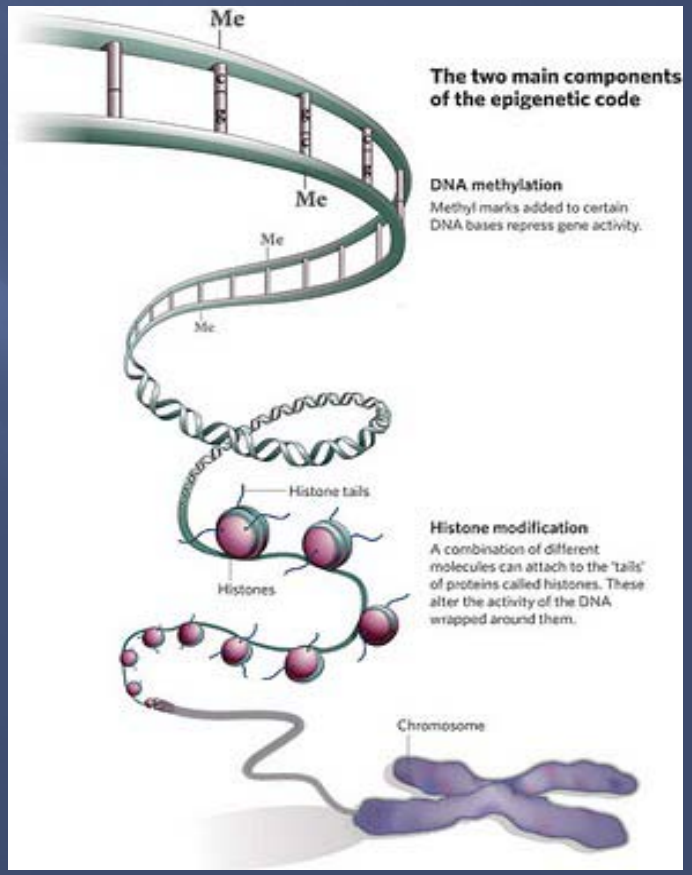
-Directly affect protein's function

The Doguck

The science of gene expression turned on or off from outside the actual DNA

Heritable changes

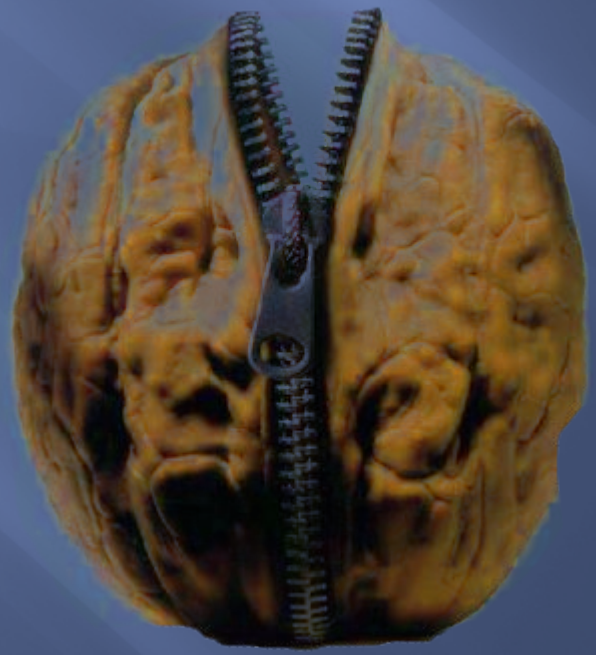
Twin studies have been revealing



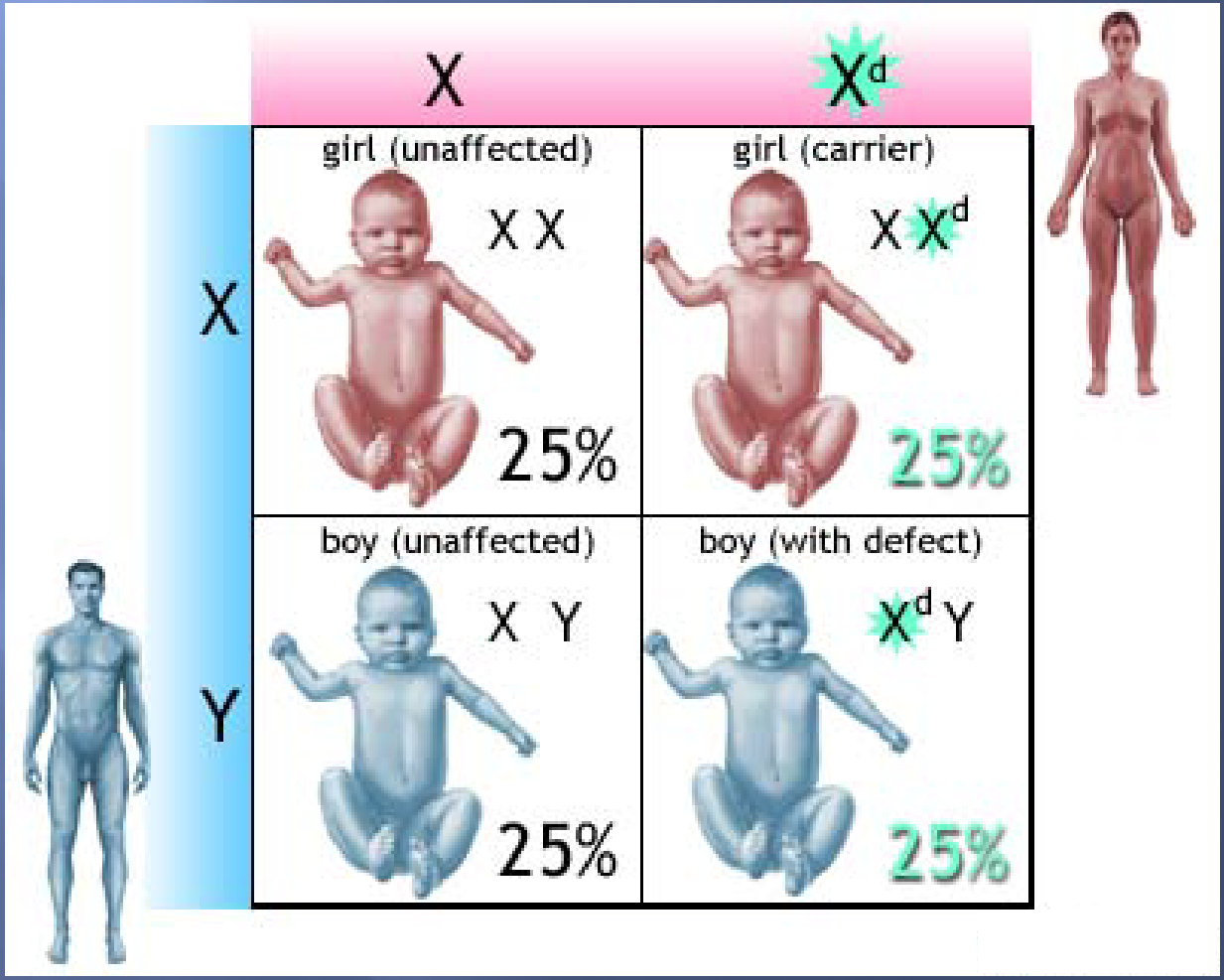
Stress
Diet
Behavior
Toxins
Other???

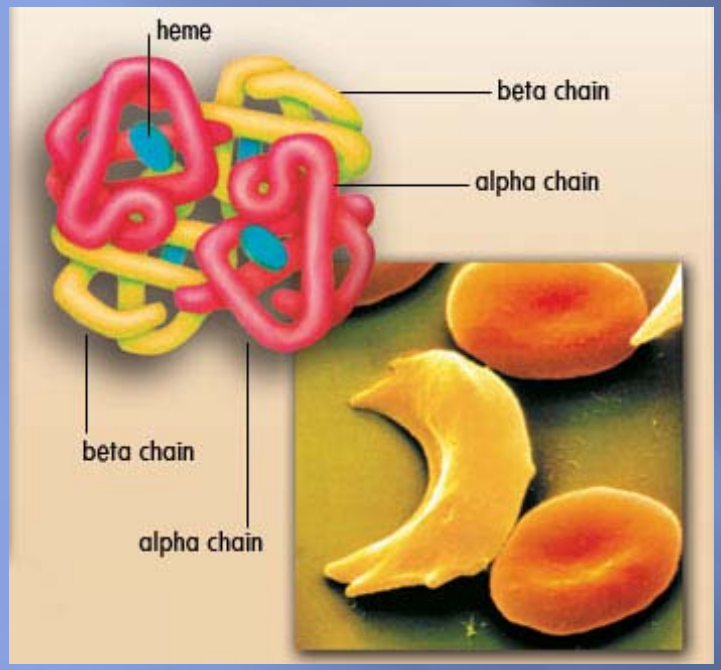
Epigenetics in a Nutshell

When the human body is put under exceptional strain a range of dormant genes in the DNA are expressed and extraordinary physiological processes are activated and can be passed on

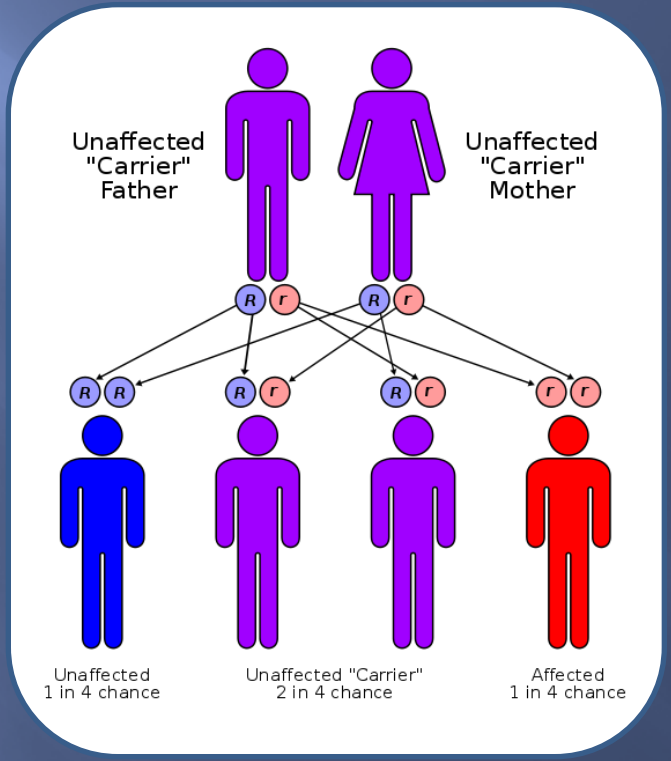


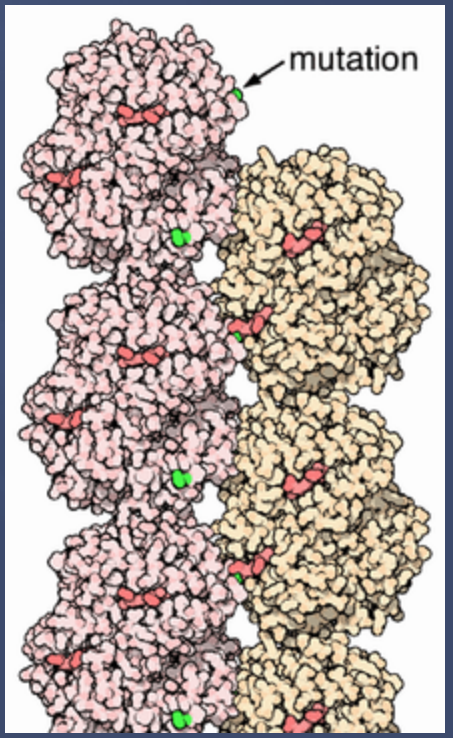
A few example disorders





- A one-point mutation in the *Beta Chain*
- Normally glutamic acid in the 6th position
- Valine replaces glutamic acid

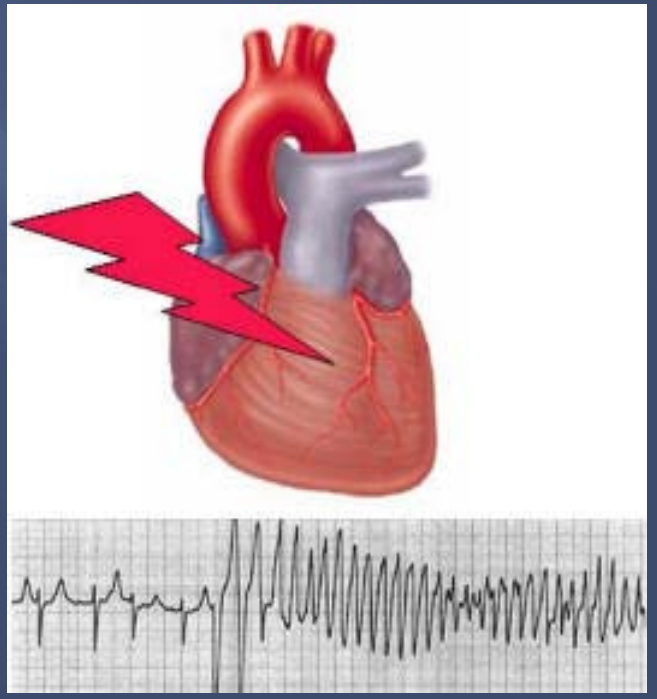




Long Q-T Syndrome

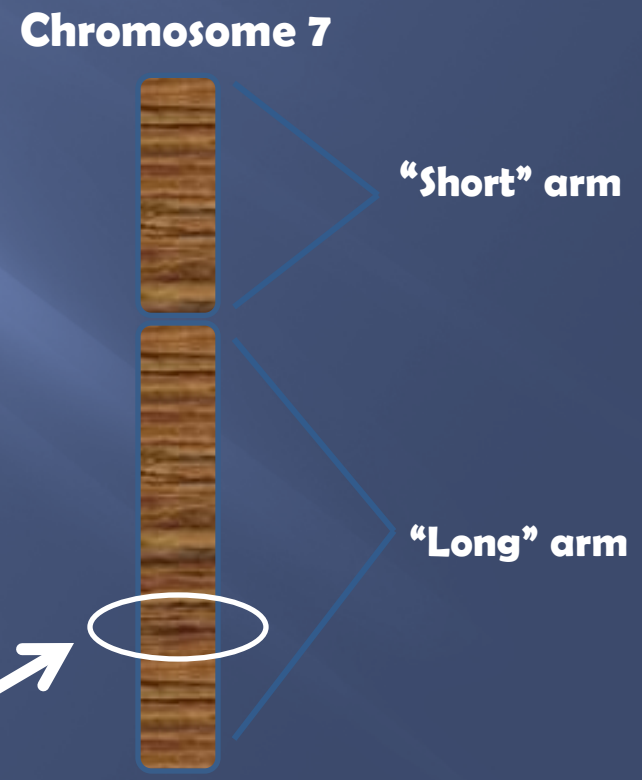
- Specific genes identified "hERG"
- Controls ion channels on cardiac cell membranes
- Though rare, numerous within-family deaths

- Specific genetic testing available
- Risk greatly reduced
  - Drug therapy
  - In-home / implanted defibrillator
  - Family resuscitation training



The defect in chromosome 7 that causes cystic fibrosis (a recessive disease—each parent must pass on)

The cystic fibrosis gene resides on chromosome 7 and normally gives rise to cystic fibrosis transmembrane conductance regulator (CFTCR). The most common defect that leads to the disease is the deletion of 3 nucleotides from the gene that results in the loss of one amino acid (*phenylalanine*) although many other defects have been identified.

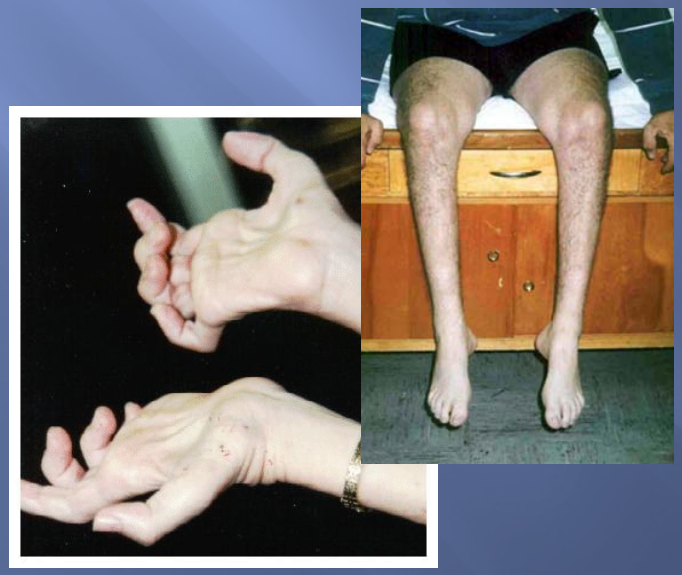


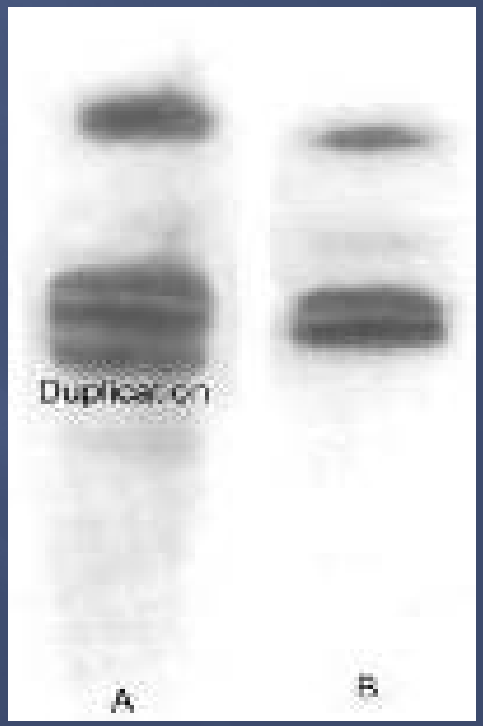
Charcot- Marie Tooth disease

(*hereditary motor & sensory neuropathy*)

- **Common 1:2500 people in U.S.**
- **Mutation of PMP22 gene (myelin protein gene)**

- **Japan 10.5 / 100k**
- **Italy 17.5 / 100k**
- **Spain 28.2 / 100k**

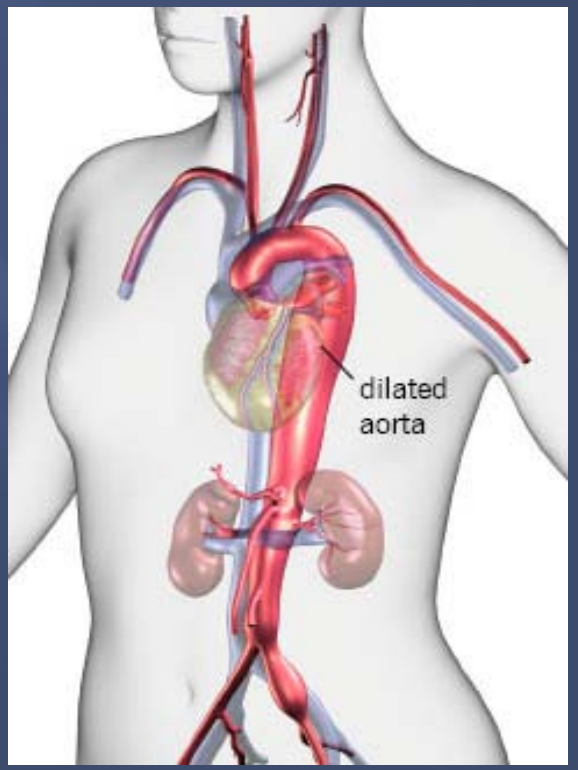




Duplication in the short arm of chromosome 17 (A) *vs* normal (B)

Marfan's Syndrome

- Enlargement and weakening of aorta
- Caused by mutation in gene for fibrillin-1
- Essential protein in connective tissue
- Integrity of
  - aorta
  - spine
  - fibers that stabilize eye lens



Pompe Disease

- Mutation in alpha-glucosidase (GAA)
- Essential to glycogen metabolism
- Glycogen accumulates
- Heart & skeletal muscle most affected

Gel-mediated Delivery of AAV1 Vectors Corrects Ventilatory Function in Pompe Mice With Established Disease

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Pompe disease is a muscular dystrophy that results in respiratory insufficiency. We characterized the outcomes of targeted delivery of recombinant adeno-associated virus serotype 1 (rAAV2/1) vector to diaphragms of Pompe mice with varying stages of disease progression. We observed significant improvement in diaphragm contractile strength in mice treated at 3 months of age that is sustained at least for 1 year and enhanced contractile strength in mice treated at 9 and 21 months of age, measured 3 months post-treatment. Ventilatory parameters including tidal volume/inspiratory time ratio, minute ventilation/expired CO_2 ratio, and peak inspiratory airflow were significantly improved in mice treated at 3 months and tested at 6 months. Despite early improvement, mice treated at 3 months and tested at 1 year had diminished normoxic ventilation, potentially due to attenuation of correction over time or progressive degeneration of nontargeted accessory tissues. However, for all rAAV2/1-treated mice (treated at 3, 9, and 21 months, assayed 3 months later; treated at 3 months, assayed at 1 year), minute ventilation and peak inspiratory flows were significantly improved during respiratory challenge. These results demonstrate that gel-mediated delivery of rAAV2/1 vectors can significantly augment ventilatory function at initial and late phases of disease in a model of muscular dystrophy.

Received 25 November 2008; accepted 10 December 2009; published online 26 January 2010. doi:10.1038/mt.2009.305

INTRODUCTION

In many forms of muscular dystrophy, the progressive weakening and wasting of skeletal muscles, and in particular the respiratory muscles, leads to ventilatory insufficiency, which oftentimes results in the need for mechanical ventilation. Pompe disease (glycogen storage disease type II; acid maltase deficiency; MIM 232300) is one form of inherited muscular dystrophy and is caused by a lack of functional lysosomal acid α-glucosidase (GAA). GAA is responsible for the breakdown of lysosomal glycogen to monosaccharides. A deficiency of GAA results in the severe storage of glycogen in lysosomal compartments of striated muscle, ultimately leading to the disruption of contractile capabilities of the cell.[1] There exists a continuum of Pompe disease that correlates with the levels of GAA enzyme activity and onset of clinical disease. In the infantile form, there is little to no residual GAA activity and those affected usually do not survive beyond 2 years of age as a result of cardiorespiratory failure. The juvenile and adult-onset forms of Pompe disease result from a partial deficiency of GAA and the primary consequence is ultimately respiratory failure.[2–6]

Recently, a recombinant GAA has been approved for use in an enzyme replacement therapy strategy for the treatment of Pompe disease. A biweekly infusion of the recombinant enzyme has been shown to improve survival in subjects with the infantile form of disease; however, many patients receiving enzyme replacement therapy eventually require assisted ventilation.[7,8] Gene therapy provides an attractive alternative to the current mode of therapy, as it could provide continuous endogenous expression of the therapeutic protein directly within the affected tissues. We, and others, have shown the potential of recombinant adeno-associated virus (rAAV) vectors for the treatment of Pompe disease.[9–17]

AAVs are nonpathogenic parvoviruses that are being widely developed as potential human gene therapy vectors. To date, over 20 different clinical trials have been initiated using rAAV vectors. Although AAV2 was used as the basis for the first AAV-based gene therapy vector, >100 different isolates of AAV have since been identified, many of which have already been developed as pseudotyped gene therapy vectors in which the rAAV2-based vector genome is encapsidated in a different serotype capsid.[18–22] Each serotype may confer differential cell type tropisms, which could be exploited for more targeted gene therapy applications.

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- Discovery of GAA gene →
- Enzyme replacement therapy → ↓ glycogen accumulation
- Targeted gene therapy

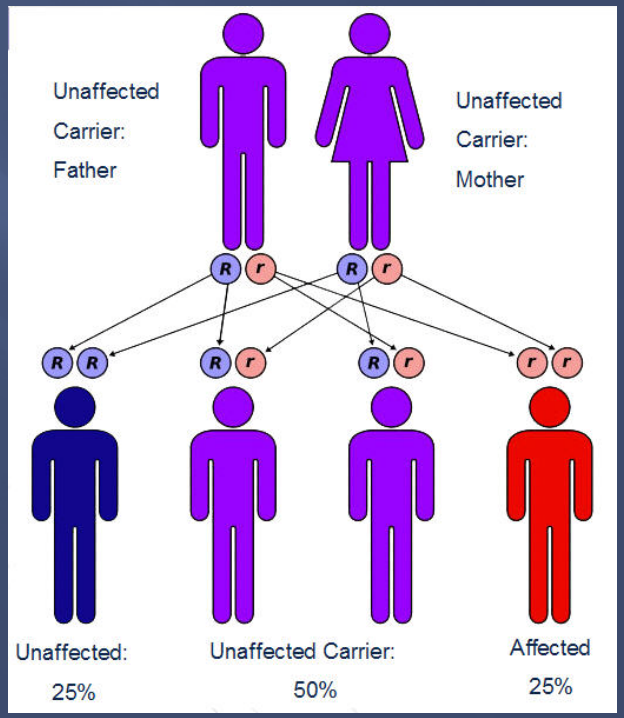
When your diet can save your life

The success story of phenlyketonuria

- Phenylalanine, essential amino acid
- Mutation→ loss of phenylalanine hydroxylase
- → brain injury

- Disease 100% genetic
- Adversity 100% preventable

- Predictable biochemical or DNA test
- 1960→ routine newborn screening



1831

Darwin's voyage continues!

An early foundation of "personalized medicine"

- **Before Darwin, species viewed as "immutable, fixed"**
- **Each member an "ideal" – each a "mirror reflection"**

- **Recognized crucial importance of *variation***

- **Today we are following Darwin's lead**
- **Scrutinizing genetic variations that make each unique**
- **When harnessed may revolutionize health care**

Alleles that predispose to ADHD, OCD and social anxiety disorders may have been highly adaptive during most of our evolutionary history

Being "laid back" may have meant being a meal for a savannah predator

Likewise, alleles that code our lust for fat & carbohydrate & to binge eat likely evolved when lack of refrigeration meant that when prey was found, humans were well advised to binge eat

Genetic variation is key to understanding a patient's response to a Rx

Clinical Investigation and Reports

Contribution of Hepatic Cytochrome P450 3A4 Metabolic Activity to the Phenomenon of Clopidogrel Resistance

Wei C. Lau, MD; Paul A. Gurbel, MD; Paul B. Watkins, MD; Charlene J. Neer, BSN, MPA; Amy S. Hopp, BS; David G.M. Carville, PhD; Kirk E. Guyer, BS; Alan R. Tait, PhD; Eric R. Bates, MD

Background—Interindividual variability of platelet inhibition after aspirin or clopidogrel administration has been described. Additionally, aspirin resistance and clopidogrel resistance occur in some individuals. Because the prodrug clopidogrel is activated by hepatic cytochrome P450 (CYP) 3A4, we hypothesized that interindividual variability in clopidogrel efficacy might be related to interindividual differences in CYP3A4 metabolic activity.

Methods and Results—Platelet aggregation was measured before and after clopidogrel treatment in 32 patients undergoing coronary artery stent implantation and in 35 healthy volunteers. The erythromycin breath test was used to measure CYP3A4 activity in vivo in 25 of the healthy volunteers. Individual platelet aggregation was studied in 10 healthy volunteers after the coadministration of clopidogrel and rifampin (a CYP3A4 inducer). Clopidogrel nonresponders, low responders, and responders were defined by a relative inhibition of adenosine diphosphate (20 μmol/L)–induced platelet aggregation of <10%, 10% to 29%, and ≥30%, respectively. Among patients, 22% were clopidogrel nonresponders, 32% were low responders, and 47% were responders. Among volunteers, 16% were nonresponders, 12% were low responders, and 72% were responders. Percent platelet aggregation after clopidogrel inversely correlated with CYP3A4 activity ($r=-0.6$, $P=0.003$). Improved platelet inhibition in volunteers resistant to clopidogrel was observed with the coadministration of clopidogrel and rifampin.

Conclusions—Clopidogrel administration results in interindividual variability in platelet inhibition, which correlates with CYP3A4 metabolic activity. Measurement of antiplatelet drug efficacy with a point-of-care device and alternative antithrombotic strategies for aspirin or clopidogrel nonresponders and low responders could reduce the incidence of thrombotic events that continue to occur despite oral antiplatelet therapy. (*Circulation*. 2004;109:166-171.)

Key Words: drugs ■ platelets ■ pharmacology

Clopidogrel, a thienopyridine derivative similar to ticlopidine, is an inhibitor of platelet aggregation induced by adenosine diphosphate (ADP).[1] Clopidogrel was approved by the United States Food and Drug Administration (FDA) in 1997 for the reduction of myocardial infarction, stroke, and vascular death in patients with recent stroke, recent myocardial infarction, or established peripheral arterial disease after the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial[2] showed superior reduction of these events with clopidogrel compared with aspirin (annual risk, 5.3% versus 5.8%; $P=0.04$). Dual antiplatelet therapy (aspirin plus clopidogrel) for acute coronary syndromes was approved by the FDA in 2002 on the basis of the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial[3] results, which showed a significant reduction in the 9-month composite end point of cardiovascular death, nonfatal myocardial infarction, or stroke versus aspirin monotherapy (9.3% versus 11.4%, $P<0.001$). Additionally, the combination of aspirin and clopidogrel is the standard antiplatelet therapy for coronary stenting,[4–7] although it has not gained formal FDA approval status.

The elucidation of the pharmacological properties of clopidogrel has lagged behind the randomized clinical trial reports. A 75-mg once-daily clopidogrel dose was used in CAPRIE because it produced inhibition of ADP-induced platelet aggregation equivalent to ticlopidine 250 mg twice daily.[2] Only later were dosing studies published,[8,9] and this work continues.[10–11] Subsequently, the active metabolite of clopidogrel, a prodrug, was identified,[12] and its noncompetitive inhibition of the platelet P2 Y_{12} ADP receptor was

Received August 29, 2003; de novo received October 9, 2003; revision received November 10, 2003; accepted November 25, 2003.
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This article originally appeared Online on January 5, 2004 (*Circulation*. 2004;109:r1–r6).
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Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000112378.09325.F9

Circulation. 2004;109:166

Plavix→ a "top 5" selling drug

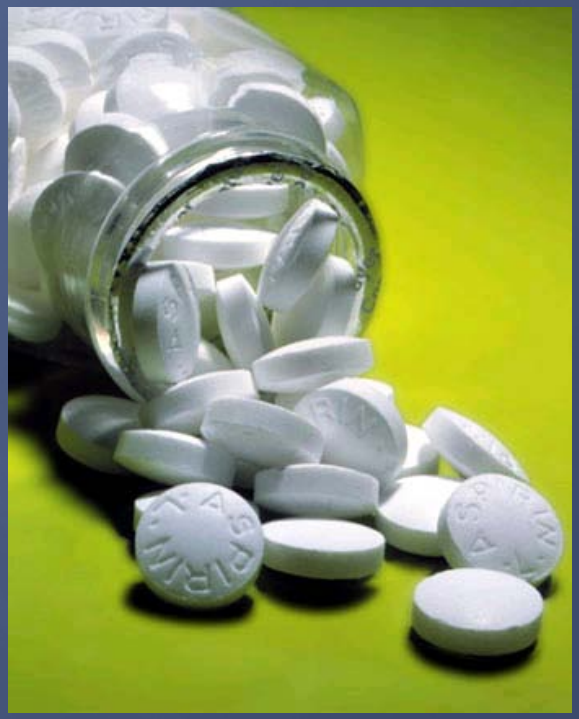
Prodrug activated by CYP2C19

In this study:
22% nonresponders
32% low responders
47% responders

FDA suggests up to 14% carry variants

Recent FDA Black Box warning regarding risk in nonresponders

JAMA. 2010;303:1587



A systematic review: aspirin response

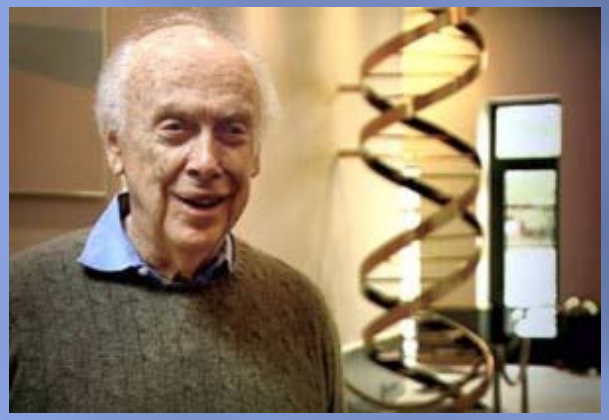
64 populations
53 different studies
6,450 subjects

Aspirin nonresponders → 27% (marked variability seen)

Crescente M et al.
Response variability to aspirin as assessed by the platelet function analyzer.
Thrombosis & Haemostasis. **2008 ;99(1):14-26.**

Why is this important for us?

- Appreciate genetic & environmental contributions
- Considerations for a non-“cookie-cutter” approach
- Explanation for variation



James Watson 1962 Nobel Laureate

2007: $2 million to sequence Watson's genome

He predicted "*a revolution if < cost of a Chevrolet*"

Today: <$4500.00 Price will continue to fall

Of current greatest interest to anesthesiology:

- **Pain**
- **Predictability of response to drugs**
- **Likelihood of adverse response**

Direct-to-consumer (DTC) genetic testing

Complete genomics

At-home test kit arrives by mail

2-3 weeks later: on-line access to one's genetic profile

Currently > 45 DTC testing companies

23andMe

DNAdirect

"Test results can help your doctor find the right drug—at the right dose—for you."

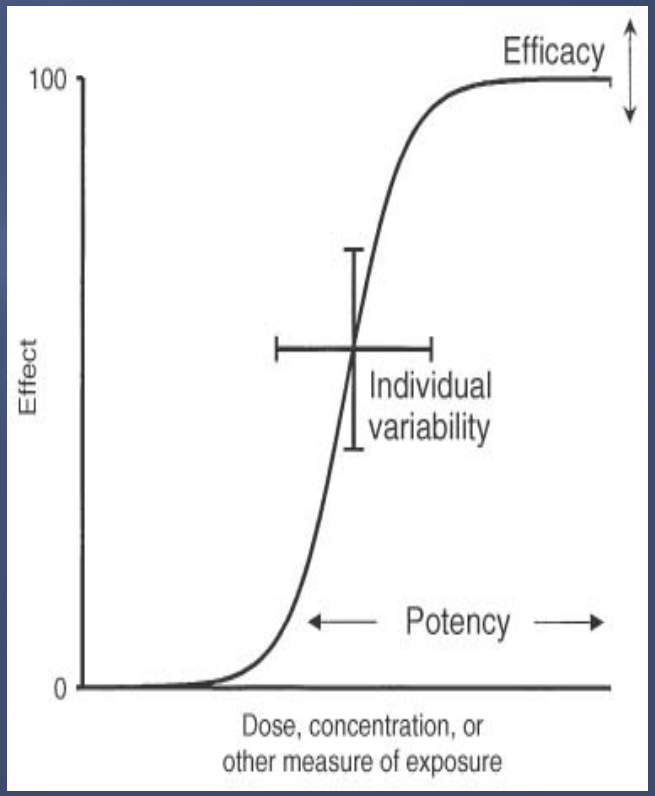
www.dnadirect.com

Pharmacokinetic *vs* Pharmacodynamic variability

- **Pharmacokinetic:** variability in absorption, distribution, metabolism or excretion

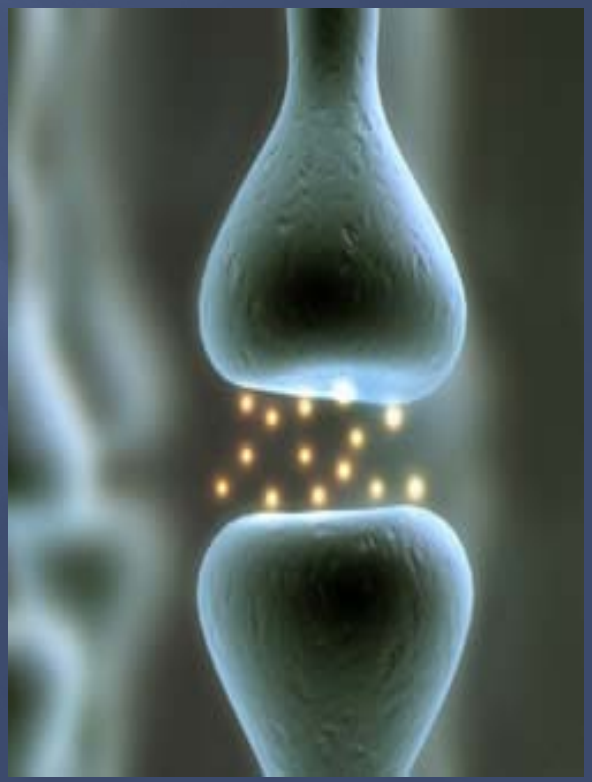
  May include metabolic enzymes
  --Cytochrome P-450 family
  --Drug transport molecules

- **Give same drug dose, see different serum concentration**



Pharmacokinetic *vs* Pharmacodynamic variability

- **Pharmacodynamic:** variability in drug effect despite equivalent drug delivery
- Variability in function or the affinity for the target
- Give same drug dose, same serum concentrations, yet different effect




2mg
2mg
COUMADIN

- Warfarin: widely prescribed oral anticoagulant
- Associated hemorrhage a leading cause of ADE/death
- Dosing extremely complex
- Highly variable response → aggressive monitoring

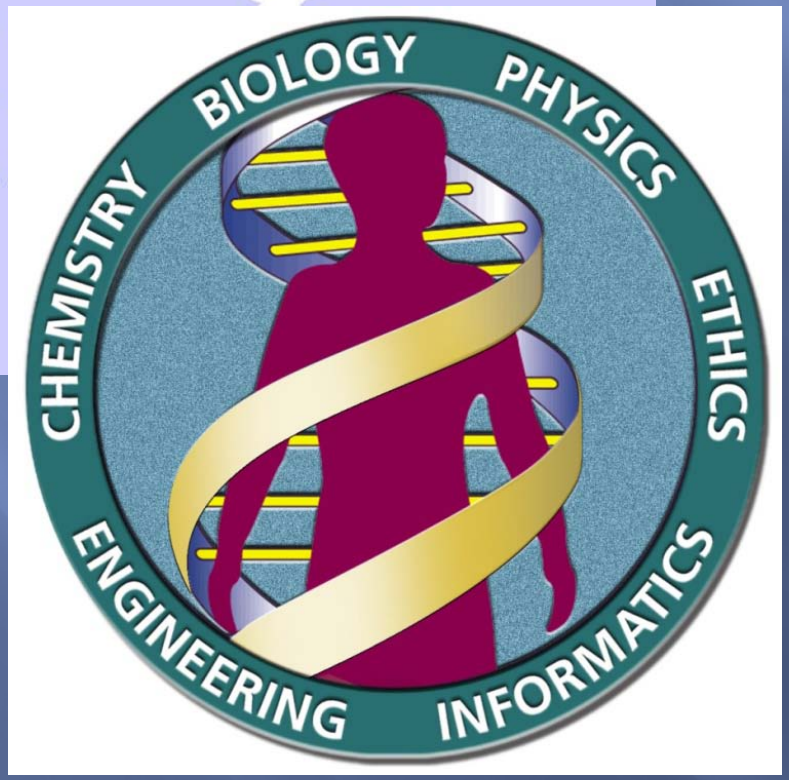
MUTATIONAL FREQUENCY ACROSS ETHNIC GROUPS

Ethnic Group	*CYP2C9*2*	*CYP2C9*3*	*VKORC1* 1173C>T
Caucasian	0.9-20%[11]	0-14.5%[11]	37%[7]
African	0.8-7%[11]	0.4-3%[11]	14%[7]
Asian	0%[11]	0-8.2%[11]	89%[7]

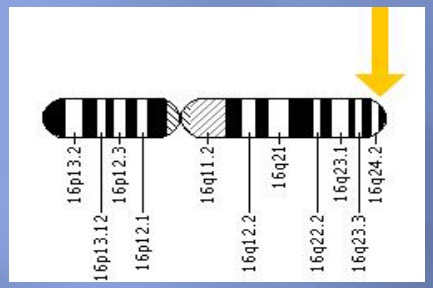
Landefeld C & Beyth R. *Am J Med* 1993; 95: 315-318
Levine M et al. *Chest* 1998; 114: 511S-523S.
Pirmohamed M et al. *BMJ* 2004; 329: 15-19
Wadelius M et al. *Pharmacogenetics* J 2005;5:262-270
Rieder MJ et al. *NEJM* 2005; 352: 2285-2293

Human Genome Project

A 3-in-1 Medical Reference



The MC1R gene provides instructions for making a protein → the melanocortin 1 receptor. This receptor plays an important role in normal pigmentation processes



Polymorphisms in the MC1R gene are associated with normal variations in skin and hair color, one being reddish hair

Anesthesiology 2004;101:279

Anesthetic Requirement Is Increased in Redheads

Edwin B. Liem, M.D., Chun-Ming Lin, M.D.,† Mohammad-Irfan Suleman, M.D.,‡ Anthony G. Doufas, M.D., Ph.D.,* Ronald G. Gregg, Ph.D.,§ Jacqueline M. Veauthier, Ph.D.,‖ Gary Loyd, M.D.,# Daniel I. Sessler, M.D.***

Background: **Age and body temperature alter inhalational anesthetic requirement; however, no human genotype is associated with inhalational anesthetic requirement. There is an anecdotal impression that anesthetic requirement is increased in redheads. Furthermore, red hair results from distinct mutations of the melanocortin-1 receptor. Therefore, the authors tested the hypothesis that the requirement for the volatile anesthetic desflurane is greater in natural redheaded than in dark-haired women.**

Methods: **The authors studied healthy women with bright red (n = 10) or dark (n = 10) hair. Blood was sampled for subsequent analyses of melanocortin-1 receptor alleles. Anesthesia was induced with sevoflurane and maintained with desflurane randomly set at an end-tidal concentration between 5.5 and 7.5%. After an equilibration period, a noxious electrical stimulation (100 Hz, 70 mA) was transmitted through bilateral intradermal needles. If the volunteer moved in response to stimulation, desflurane was increased by 0.5%; otherwise, it was decreased by 0.5%. This was continued until volunteers "crossed over" from movement to nonmovement (or *vice versa*) four times. Individual logistic regression curves were used to determine desflurane requirement (P_{50}). Desflurane requirements in the two groups were compared using Mann–Whitney nonparametric two-sample test; $P < 0.05$ was considered statistically significant.**

Results: **The desflurane requirement in redheads (6.2 vol% [95% CI, 5.9–6.5]) was significantly greater than in dark-haired women (5.2 vol% [4.9–5.5]; $P = 0.0004$). Nine of 10 redheads were either homozygous or compound heterozygotes for mutations on the melanocortin-1 receptor gene.**

Conclusions: **Red hair seems to be a distinct phenotype linked to anesthetic requirement in humans that can also be traced to a specific genotype.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

* Assistant Professor, OUTCOMES RESEARCH™ Institute and Department of Anesthesiology, † Resident, # Associate Professor, Department of Anesthesiology. § Associate Professor, Department of Biochemistry, ** Vice Dean for Research, Director OUTCOMES RESEARCH™ Institute, Distinguished University Research Chair, Lolita & Samuel Weakley Professor of Anesthesiology and Pharmacology, University of Louisville. † Research Fellow, Department of Anaesthesiology, Chang Gung Memorial Hospital, Taipei, Taiwan, R.O.C. ‖ Research Associate, Department of Chemistry and Biochemistry, University of Texas.

Received from the OUTCOMES RESEARCH™ Institute and the Departments of Anesthesiology, Biochemistry and Molecular Biology, and Pharmacology and Toxicology, University of Louisville, Louisville, Kentucky, and the Department of Chemistry, University of Texas, Austin, Texas. Submitted for publication September 9, 2003. Accepted for publication December 8, 2003. Supported by grant No. GM 061655 from the National Institutes of Health, Bethesda, Maryland; the Joseph Drown Foundation, Los Angeles, California; and the Commonwealth of Kentucky Research Challenge Trust Fund, Louisville, Kentucky. Dr. Veauthier is the recipient of an Postdoctoral Fellowship (F32 GM20834) from the National Institutes of Health, Bethesda, Maryland. None of the authors have any financial interest in products related to this study. These data were presented in abstract form at the Annual Meeting of the American Society of Anesthesiologists, Orlando, Florida, October 12–16, 2002.

Address reprint requests to Dr. Sessler: OUTCOMES RESEARCH™ Institute, 501 East Broadway, Louisville, Kentucky 40202. Address electronic mail to: sessler@louisville.edu. On the World Wide Web: www.or.org. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

INHALATIONAL anesthetic requirements are remarkably uniform in humans, mainly being affected by age and body temperature.[1,2] However, some anesthesiologists share an anecdotal impression that patients with natural red hair require more anesthesia than patients with other hair colors. The phenotype of nearly all red-haired individuals can be traced to distinct mutations of the melanocortin-1 receptor gene (*MC1R*).[3–5]

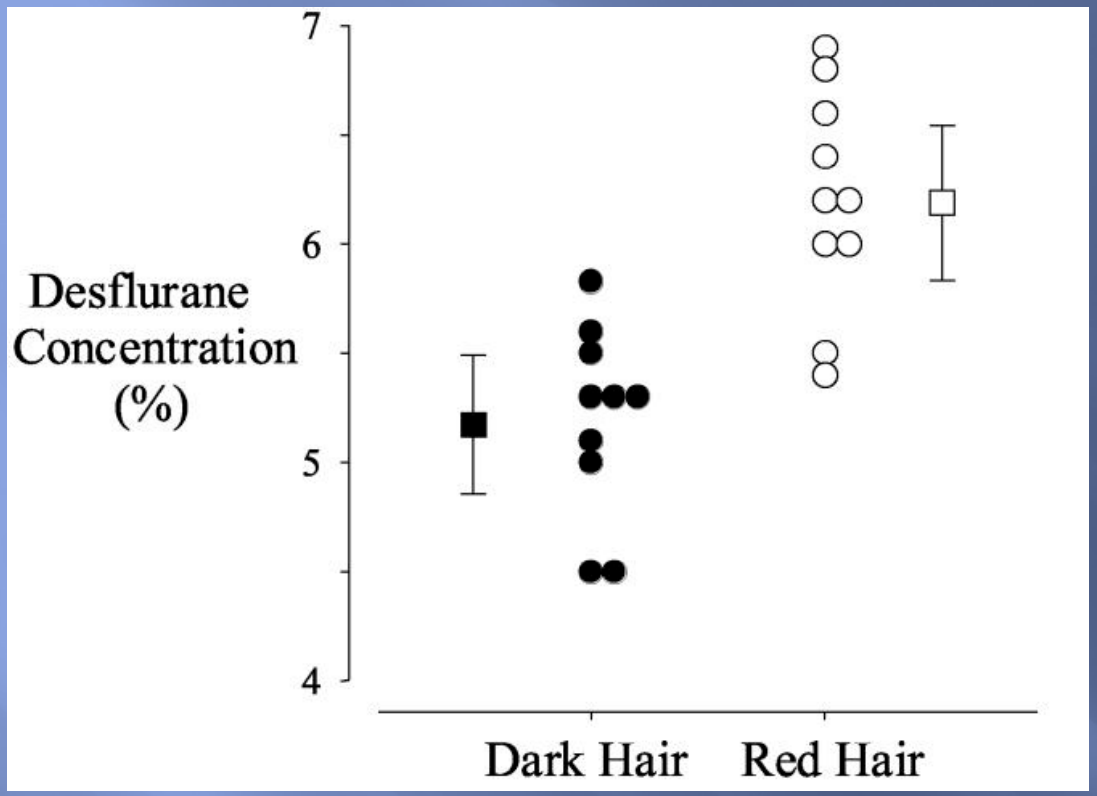
The human MC1R is expressed on the surface of melanocytes and is a key regulator of intracellular signaling to the melanin biosynthetic pathway governing pigment formation. The red hair phenotype results from excess pheomelanin production. Production of this yellow-red pigment results from well-described mutations of the *MC1R*.[3–6] In contrast, when a normal (consensus) MC1R is expressed, the predominant pigment produced by melanocytes is eumelanin (dark brown) and the typical eumelanin-to-pheomelanin ratio is high.

An easily identifiable human phenotype that can be traced to a distinct genotype presents an opportunity to identify a genetic influence on anesthetic sensitivity in humans. Distinct genetic factors have been shown to contribute to anesthetic requirements in various animal species, including mice,[7] nematodes (*Caenorhabditis elegans*),[8] and fruit flies (*Drosophila melanogaster*).[9] However, a similar association has yet to be established in humans. Therefore, we tested the hypothesis that women with natural red hair have a greater desflurane requirement than women with dark hair.

Materials and Methods

With approval of the University of Louisville Human Studies Committee and written informed consent, we recruited 20 white women aged between 18 and 40 yr, with natural bright red or dark (black or dark brown) hair. The study subjects were regarded as white if they were mainly of northern European descent as indicated by self-report. The subjects were drawn from Greater Louisville, Kentucky, an urban area with a population exceeding 1,000,000. The number of subjects was based on an *a priori* estimate that 10 subjects in each group would provide 90% power for detecting a 0.8% difference in desflurane requirement (*e.g.*, 5.8% to 5.0%) between the two groups using a two-tailed, unpaired *t* test with an α of 0.05 and an estimate of the SD of 0.55.

Because it remains unclear whether sex could cause



Analogue of MAC used in this study by applying repeated noxious electrical stimulation

The *MC1R* is also found in human pituitary tissue, glial cells, and in the human periaqueductal gray matter

PONV and CYP-450

Many antiemetics → P450 metabolism

5-HT_3 (ondansetron) → CYP2D6

--Polymorphism → efficacy increased / decreased

The Impact of Pharmacogenomics on Postoperative Nausea and Vomiting

Do CYP2D6 Allele Copy Number and Polymorphisms Affect the Success or Failure of Ondansetron Prophylaxis?

Keith A. Candiotti, M.D.,* David J. Birnbach, M.D.,† David A. Lubarsky, M.D., M.B.A.,‡ Fani Nhuch, M.D.,§ Aimee Kamat, M.D.,§ Walter H. Koch, Ph.D.,‖ Michele Nikoloff, Ph.D.,# Lin Wu, Ph.D.,** David Andrews, M.D.††

Background: **Some patients treated with ondansetron for postoperative nausea and vomiting do not respond to therapy. One possible mechanism for this failure is ultrarapid drug metabolism via the cytochrome P-450 system, specifically the enzyme 2D6 (CYP2D6). Ultrarapid metabolism is seen in patients with multiple functional copies (≥ 3) of the CYP2D6 allele. This study was designed to determine whether patients who were given prophylactic ondansetron and had multiple CYP2D6 alleles had an increased rate of postoperative nausea and vomiting.**

Methods: **Two hundred fifty female patients undergoing standardized general anesthesia were given 4 mg ondansetron 30 min before extubation. Patients were observed for symptoms of nausea and vomiting. DNA was extracted from blood in all patients and was analyzed by using a gene-specific probe to determine the CYP2D6 gene copy number and genotyped by polymerase chain reaction amplification with a custom oligonucleotide microarray to determine the specific CYP2D6 genotypes.**

Results: **Eighty-eight patients experienced nausea, and 37 of those patients also had vomiting. In patients with one, two, or three CYP2D6 copies, the incidences of vomiting were 3 in 33 (27%), 27 in 198 (14%), and 7 in 23 (30%), respectively. The incidence of vomiting in subjects with three CYP2D6 copies was significantly different from those with two copies, but not from those with one copy. When analyzed by genotype, the incidences of vomiting in poor, intermediate, extensive, and ultrarapid metabolizers were 1 in 12 (8%), 5 in 30 (17%), 26 in 176 (15%), and 5 in 11 (45%), respectively ($P < 0.01$ *vs.* all other groups). There were no differences between groups in the incidence of nausea based on CYP2D6 copy number or genotype.**

Conclusions: **Patients with three copies of the CYP2D6 gene, a genotype consistent with ultrarapid metabolism, or both have an increased incidence of ondansetron failure for the prevention of postoperative vomiting but not nausea.**

POSTOPERATIVE nausea and vomiting (PONV) is a frequent and unpleasant experience for patients undergoing surgery during general anesthesia. Approximately 20–40% of surgical patients experience PONV,[1] with certain high-risk groups having a PONV incidence as high as 80%.[2] The introduction of 5-hydroxytryptamine ($5\text{-}HT_3$) receptor antagonists for the treatment of PONV and chemotherapy-induced nausea and vomiting (CINV) has revolutionized the care of surgery patients and chemotherapy patients. However, although the $5\text{-}HT_3$ antagonists have significantly reduced PONV, they have not totally eliminated it. For example, in several studies, high-risk patients were given a single $5\text{-}HT_3$ antagonist, ondansetron, for prophylaxis of PONV, but patients still had a PONV rate of greater than 35%.[3,4] There are several mechanisms that can readily explain $5\text{-}HT_3$ treatment failures, the most likely being the fact that PONV is multifactorial involving factors other than serotonin.[5] This is illustrated by the fact that multimodal PONV therapies directed against multiple targets have significantly increased efficacy over monotherapies.[6] This stands in contrast to CINV, which is mainly brought about by the release of serotonin and substance P.[7] Another cause for interindividual variations in drug response in the treatment of PONV may be variations in drug biotransformation by genetically polymorphic enzymes, such as the hepatic cytochrome P-450 enzyme 2D6 (CYP2D6).[8] All of the currently used $5\text{-}HT_3$ antagonists are metabolized *via* cytochrome P-450 enzymes. It seems that the P-450 system has limited endogenous substrates and their primary function is the metabolism of dietary components, including drugs.[9] CYP2D6 is responsible for the majority of the metabolism of dolasetron and tropisetron[10] and partially responsible for the metabolism of ondansetron, which is also broken down by the enzymes CYP3A4, CYP2E1, and CYP1A2.[11] In contrast, granisetron, another $5\text{-}HT_3$ antagonist, is primarily metabolized by CYP3A4, with no contribution from CYP2D6.[12]

CYP2D6 has a large number of reported polymorphisms and alleles that result in various phenotypic expressions of increased, decreased, or absent enzymatic activity.[13] Based on phenotypic behavior, the wild-type alleles are considered CYP2D6*1, CYP2D6*2, and CYP2D6*35. CYP2D6 activity may be classified into one of four categories: poor metabolizers (no enzyme production, with two deficient alleles), intermediate me-

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Received from the Department of Anesthesiology, Perioperative Medicine and Pain Management, and the Department of Pathology, University of Miami School of Medicine, Miami, Florida, and the Department of Pharmacogenetics, Roche Molecular Systems, Pleasanton, California. Submitted for publication September 1, 2004. Accepted for publication November 10, 2004. Supported in part by a grant from Roche Labs Inc., Nutley, New Jersey. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 23–27, 2004.

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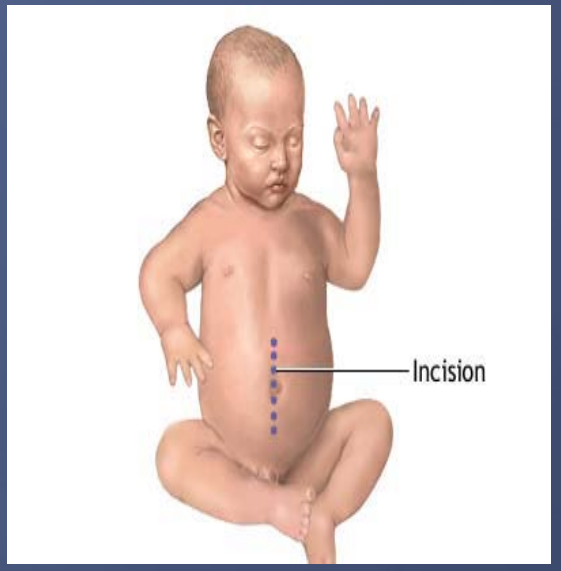
A1597
October 19, 2009
ASA Annual Meeting, Research Presentations

ABCB1 Gene Modulates the Intensity of Postoperative Pain in Children

Hôpitaux Universitaires de Genève, Switzerland



Powerful association between the *ABCB1* gene and intensity of postop pain

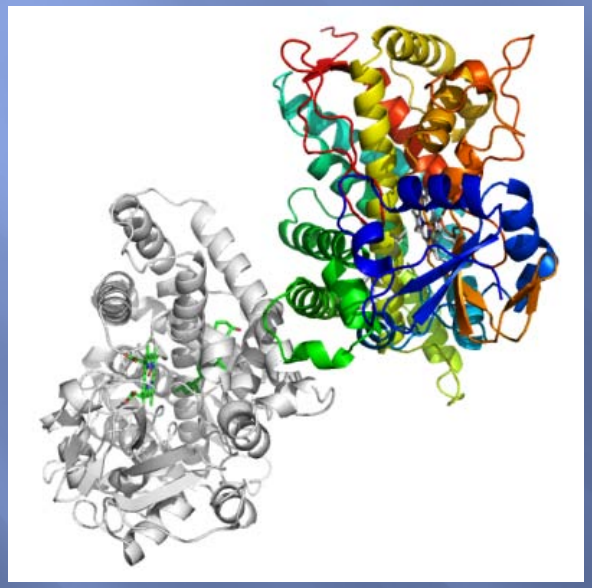
137 children, 4-16 yo, orthopedic or general surgery

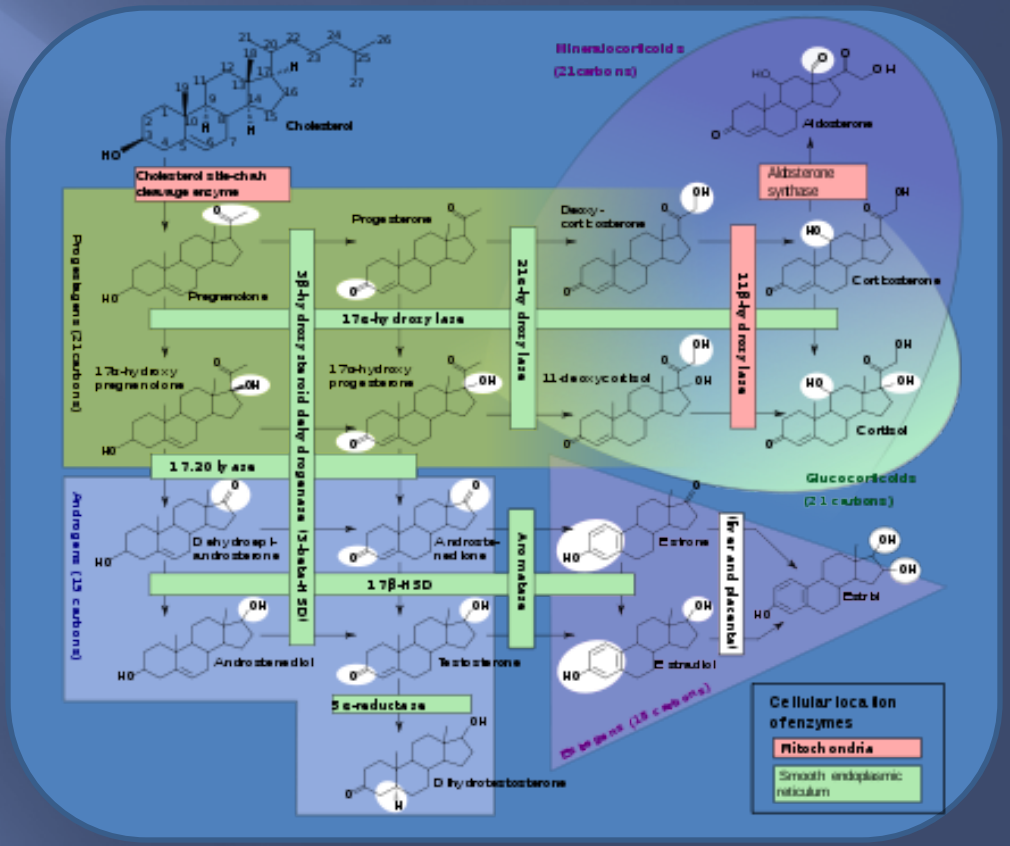
100 known *ABCB1* polymorphisms

→ altered pain perception & opioid effects in CNS

Cytochrome P450 Enzyme Family
--A large and diverse group--

- **Membrane bound hemoproteins that catalyze the oxidation of organic compounds**



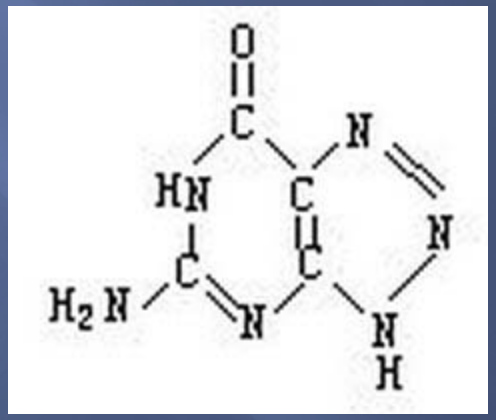


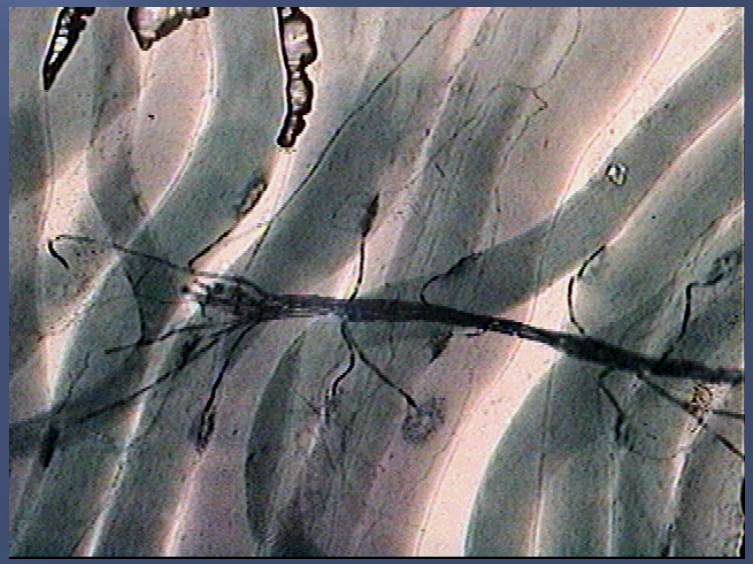
Steroidogenesis by P450 enzymes

Neuromuscular blocking agents

- Effectiveness strongly associated with genetics

- First published article on pharmacogenetics??
- Case reports of prolonged paralysis with Sch





Anesthesiology 2005; 102:531–5

Genotyping the Butyrylcholinesterase in Patients with Prolonged Neuromuscular Block after Succinylcholine

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Background: **Succinylcholine remains the standard neuromuscular blocking drug for tracheal intubation in emergency situations. The short duration of action is due to its rapid hydrolytic degradation by butyrylcholinesterase (plasmacholinesterase). Multiple variants of this enzyme are known (A, F, S, H, J, K variants) with different effects on enzyme activity. This study was undertaken to evaluate the use of molecular genetic methods in patients with clinically prolonged neuromuscular block.**

Methods: **Nine patients with a neuromuscular block of 14 min to 5 h were selected. All four exons of the butyrylcholinesterase were amplified by polymerase chain reaction and analyzed by automated sequencing. Molecular genetic results were compared with clinical relaxation time and with biochemical test results (total butyrylcholinesterase activity, dibucaine and fluoride inhibition).**

Results: **Seven of nine patients were mutation carriers. Five of these had more than one mutation. The A and K variants were the most frequent variations. Three of four patients who were homozygous for the A variant were also carriers of the K allele. The authors identified one novel mutation (G1294T) introducing a stop codon at amino acid position 432. The duration of neuromuscular block was substantially different between patients with identical butyrylcholinesterase genotypes.**

Conclusions: **Variations in the genetic sequence of butyrylcholinesterase are frequent in patients with prolonged duration of action of succinylcholine. Direct sequencing of the whole butyrylcholinesterase gene is an appropriate method for genotyping and, accordingly, should be used in future clinical studies with drugs metabolized by this enzyme (e.g., succinylcholine, mivacurium).**

SUCCINYLCHOLINE remains the drug of first choice for facilitating tracheal intubation in emergency patients and in patients with a high risk of gastroesophageal regurgitation.[1–4] The short duration of action of succinylcholine is due to its rapid hydrolization by the enzyme butyrylcholinesterase (BCHE; benzoylcholinesterase, plasmacholinesterase, pseudocholinesterase, acylcholine acylhydrolase).

A remarkably prolonged duration of action of succinylcholine in some patients led to the discovery of one of the first pharmacogenetic disorders, called *postanesthetic apnea*.[5] Besides the usual (U) variant of BCHE, three qualitative variants with altered hydrolyzing activity were identified: the atypical (A), fluoride-resistant (F), and silent (S) variants. In addition, three quantitative variants (H, J, and K) with decreased enzyme concentration but normal activity have been described (table 1).[6] Biochemical methods use butyrylcholine as an *in vitro* substrate for BCHE, and total BCHE activity as well as enzyme inhibition by dibucaine or fluoride is measured. The A and F variants are characterized by normal total activity *in vitro* but reduced inhibition by dibucaine and fluoride, respectively. Although thousands of patients have been investigated by these biochemical methods and "genotyped" according to BCHE activity and inhibition,[7] genotyping by biochemical methods is known to be inadequate.[8–10]

The identification of a single gene locus encoding for BCHE on chromosome 3q26 allowed molecular genetic techniques to be used for investigations in patients with reduced BCHE activity.[11,12] A variety of mutations responsible for most variants has been published.[6,9] However, only limited data are available describing the relation between clinical data, *i.e.*, duration of neuromuscular block by succinylcholine, biochemical analyses, and molecular genetic investigations.

In the current study, we analyzed the sequence of BCHE gene in patients with prolonged duration of action of succinylcholine. The aim was to investigate the adequacy of patient selection with possible BCHE deficiency on the basis of simple clinical criteria and to compare phenotypic representation and molecular genetic results in these subjects. We also wanted to determine the feasibility and advantages of full-length sequencing of the BCHE gene over a screening program for known mutations only.

Materials and Methods

Patient Selection

The local ethics committee (ethical commission of Basel, Switzerland) approved the study protocol. Members of the study group selected patients having a prolonged duration of action of succinylcholine during routine anesthetic practice. Neuromuscular function was measured using continuous 1-Hz single-twitch supramaximal stimulation at the ulnar nerve and tactile monitoring of the adductor pollicis longus by the anesthesiologist in charge. The time from injection of succinylcholine until initial twitch response was measured. Duration of more than 10 min was defined as

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Received from the Departments of Anesthesia and Research, University Hospital, University of Basel, Basel, Switzerland. Submitted for publication September 1, 2004. Accepted for publication October 25, 2004. Supported by the Department of Anesthesia, Anästhesieverein, Basel, Switzerland, and the Swiss Association for Anesthesia and Resuscitation, Bern, Switzerland. Presented in part as a poster at the 77th Annual Meeting of the International Anesthesia and Research Society, New Orleans, Louisiana, March 25, 2003, and awarded the Best of Meeting Award.

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Discovery of perhaps the first known pharmacogenetic disorder

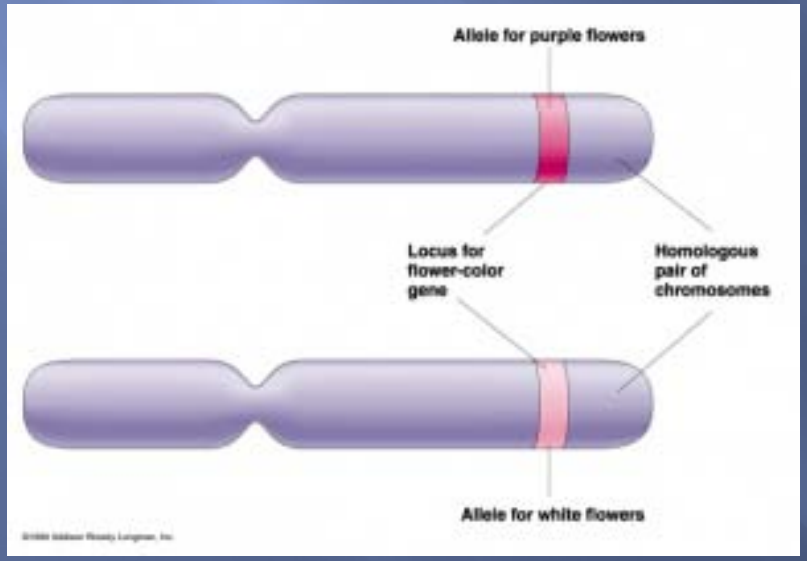
Kalow W.
J Pharmacol Exp Ther 1957; 120:203

Table 1. The Variants of Butyrylcholinesterase

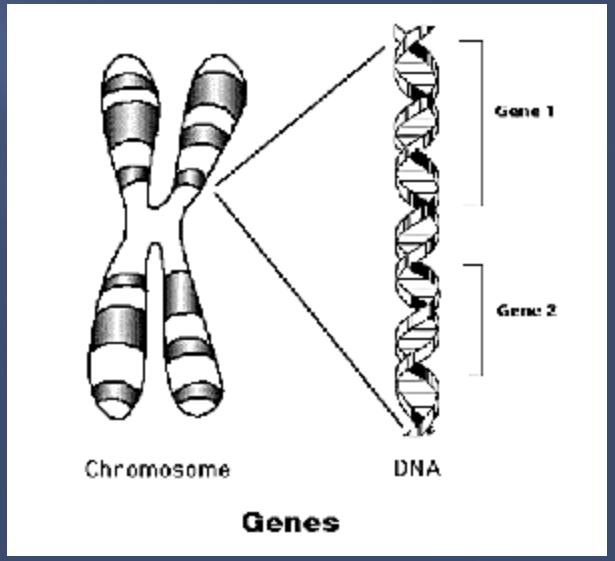
Name	Abbreviation	Mutation	Allele Frequency	Description
Usual	U		0.85	Normal
Atypical	A	A209G	0.018	Reduced activity, dibucaine resistant
Fluoride resistant	F	C728T, G1169T	0.002	Reduced activity, fluoride resistant
Silent	S	Multiple	?	No activity
H	H	G424A	?	Approximately 10% reduced concentration
J	J	A1490T	0.002	Approximately 33% reduced concentration
K	K	G1615A	0.128	Approximately 66% reduced concentration

Neuromuscular blocking agents

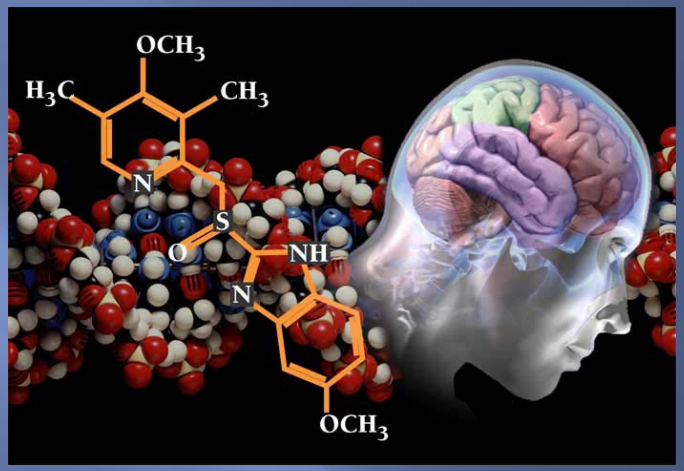
- Inherited variation of drug metabolism involving cholinesterase
- Heterozygotes → 3-8 x normal recovery period
- Homozygotes→ up to 60 x normal recovery time



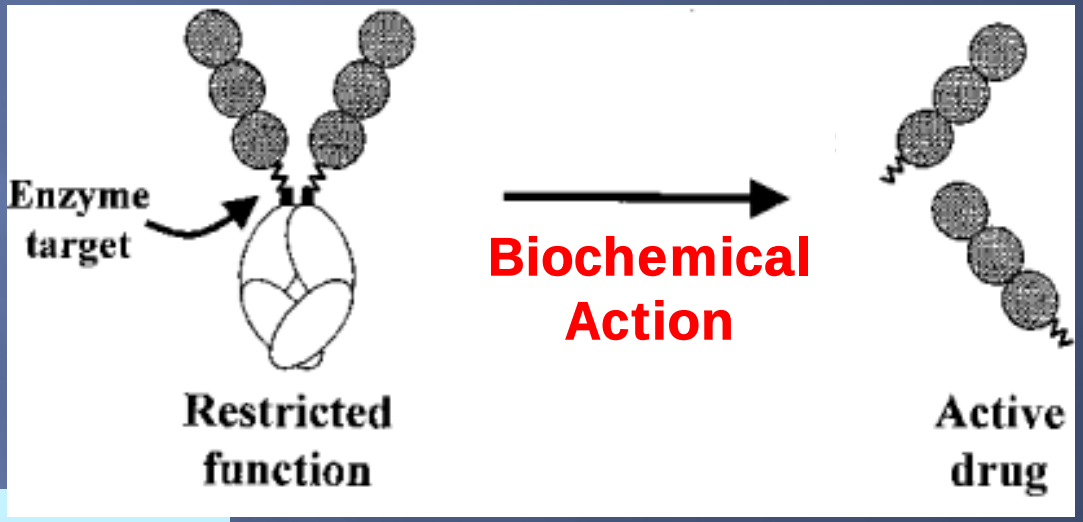
Allele:
the genes found at the same locus on different homologous chromosomes

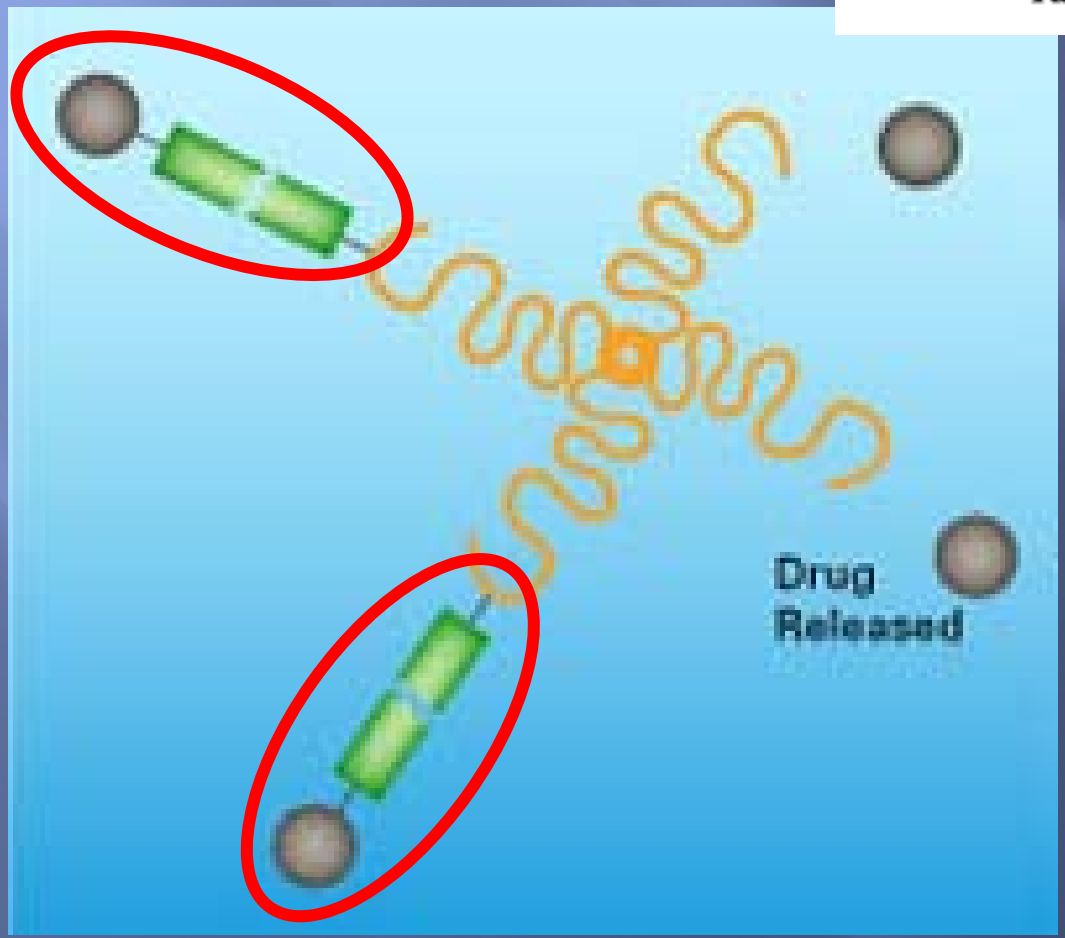


Benzodiazepines



- Half-life dependent upon cytochrome P-450 system
  - CYP2C19, CYP3A4, CYP3A5
- Polymorphism→ 4x longer $T_{1/2}$ of diazepam in homozygotes
- Midazolam variability has weaker association, has means of clearance other than P-450 system

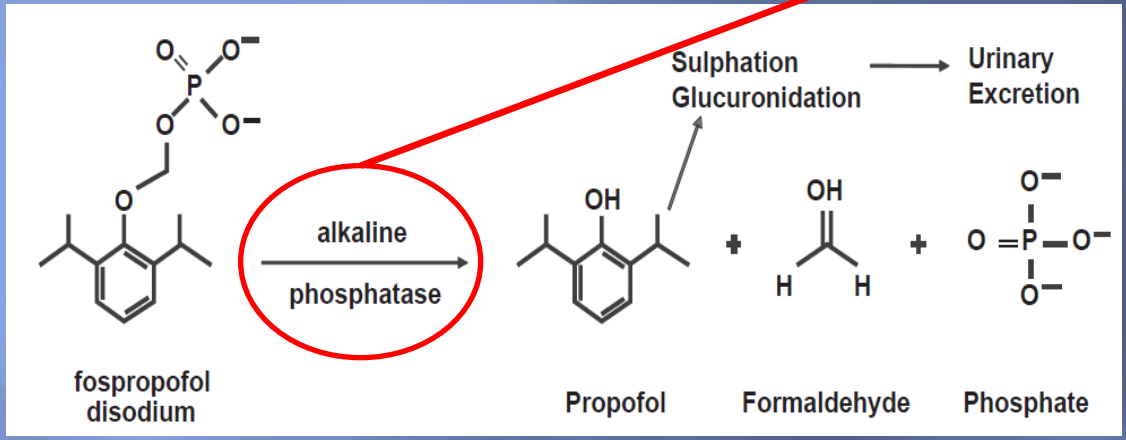




The Prodrug Concept

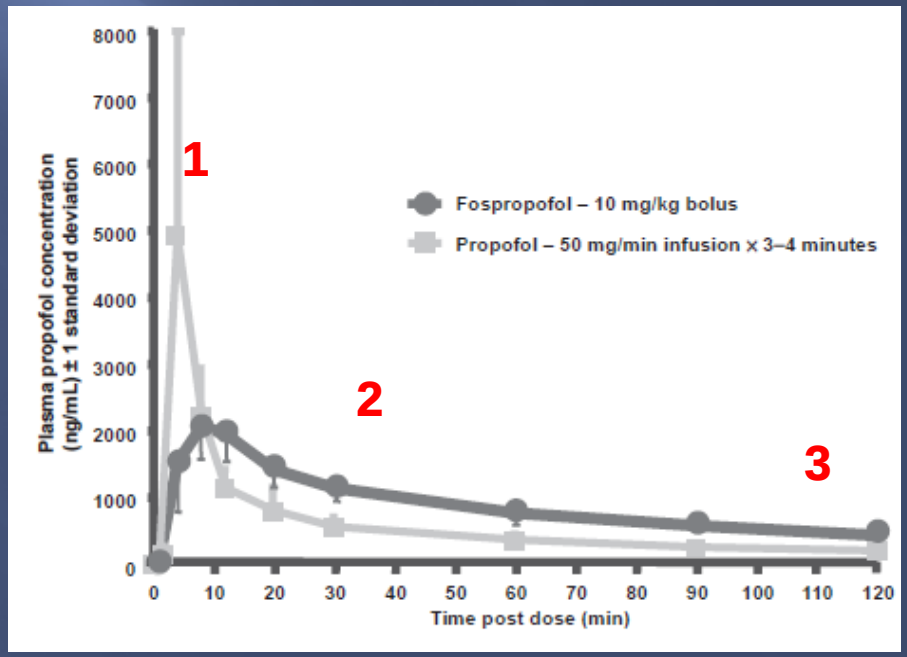
Fospropofol

>190 known mutations of the producing gene



Propofol kinetics

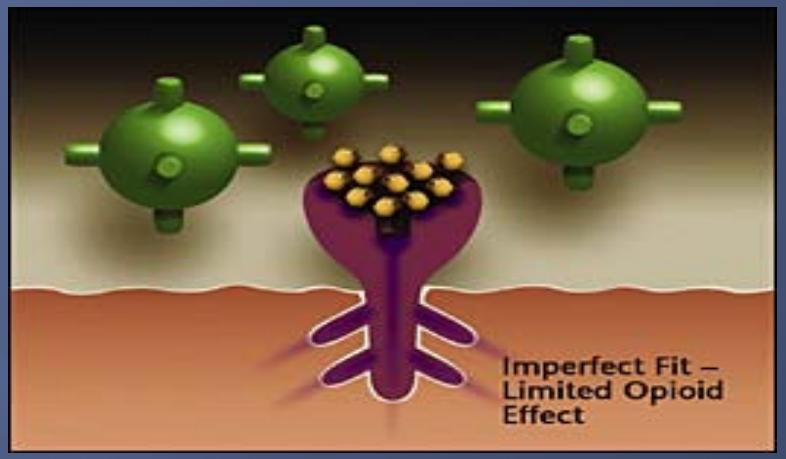
1. Redistribution (fast!)
2. Metabolism (30-60 mins)
3. Metabolism from VPG (2-45 hrs)



Opioids

- **Mu receptor variant** associated with decreased adverse effects (N/V, sedation) with morphine
- **Large inter-individual differences**
- P-450 polymorphism (CYP2D6)
  Pro-drug codeine→ morphine
  Nonresponders→ 0.5% China, 29% Ethiopia, 5% US

Opioids



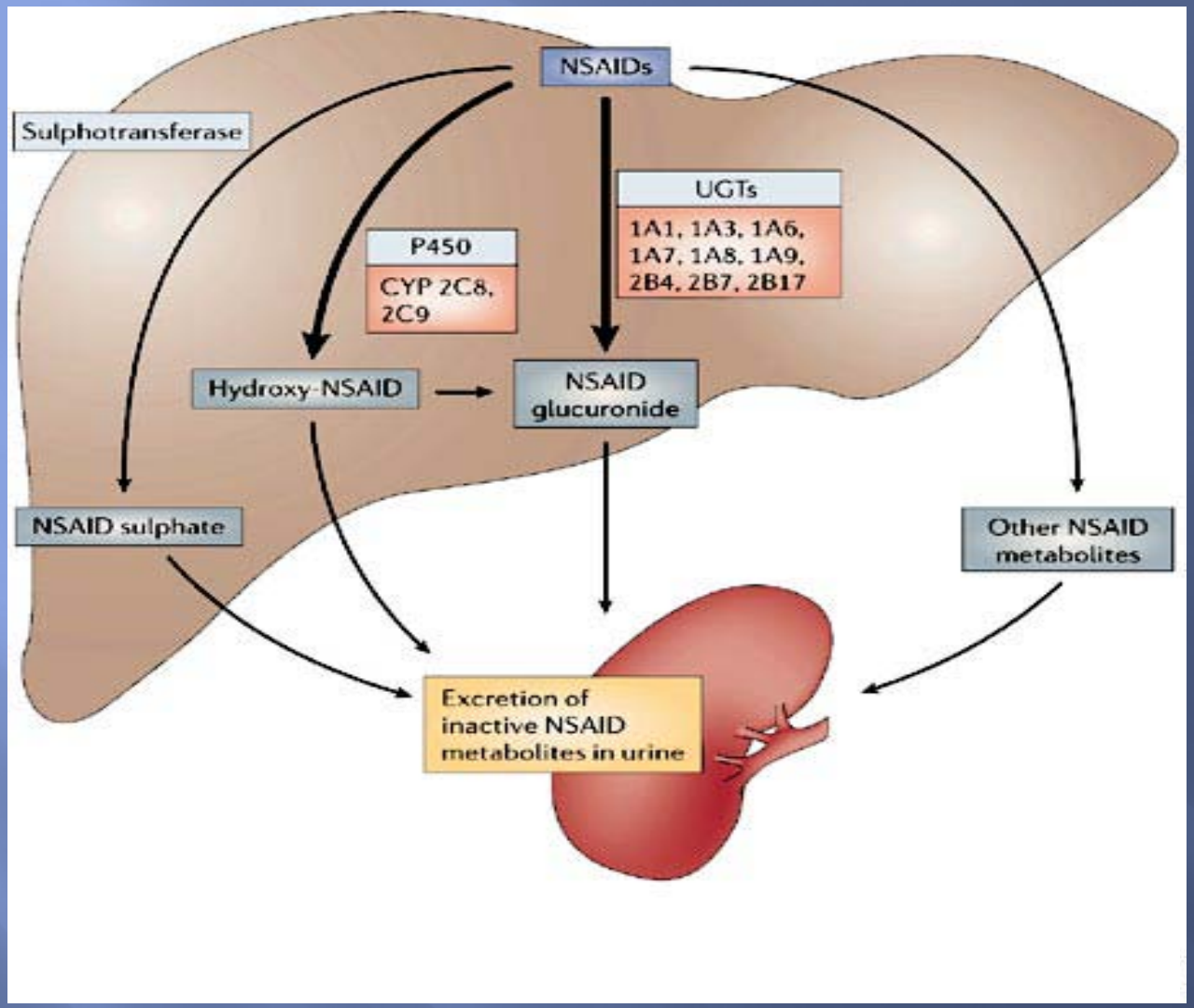
- Genelex (Seattle) advertises testing for CYP2D6 implying knowledge→ correct pain Rx

- COMT degrades norepi and dopamine
- Mutation→ altered pain sensitivity

- Would knowledge→ better insight and Rx?

NSAIDS

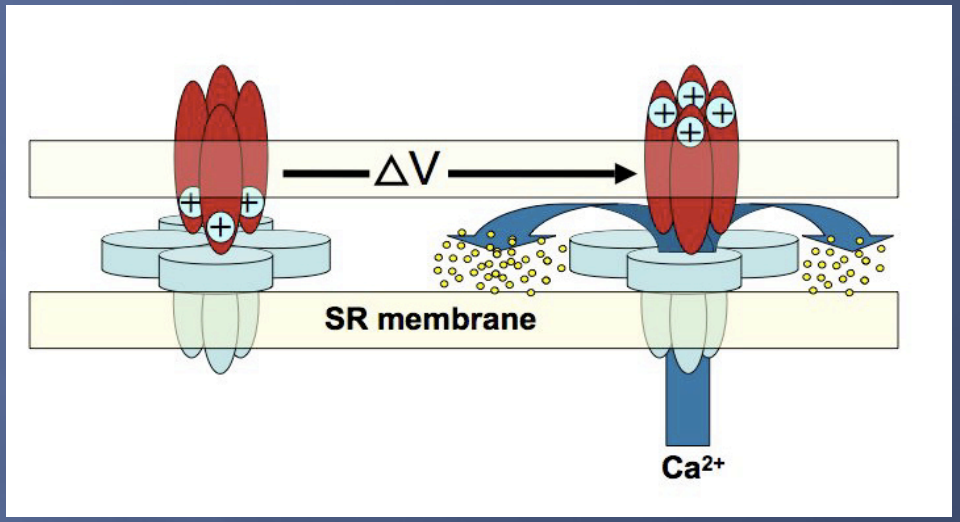
- Many metabolized by cytochrome enzymes
- Metabolism significantly slowed or speeded in individuals with specific allele variation



All are *gene based processes*

The major metabolic pathways for NSAID inactivation and elimination are via the cytochrome P450 enzymes, glucoronide conjugation, and sulphate conjugation

Volatile Anesthetics: MH



Primary efflux pathway for Ca^{++} release from SR

- Disorder of skeletal muscle Ca^{++} metabolism
- Triggered by administration of volatile agent/Sux

- Susceptibility linked to ryanodine receptor locus
- > 23 different associated polymorphisms

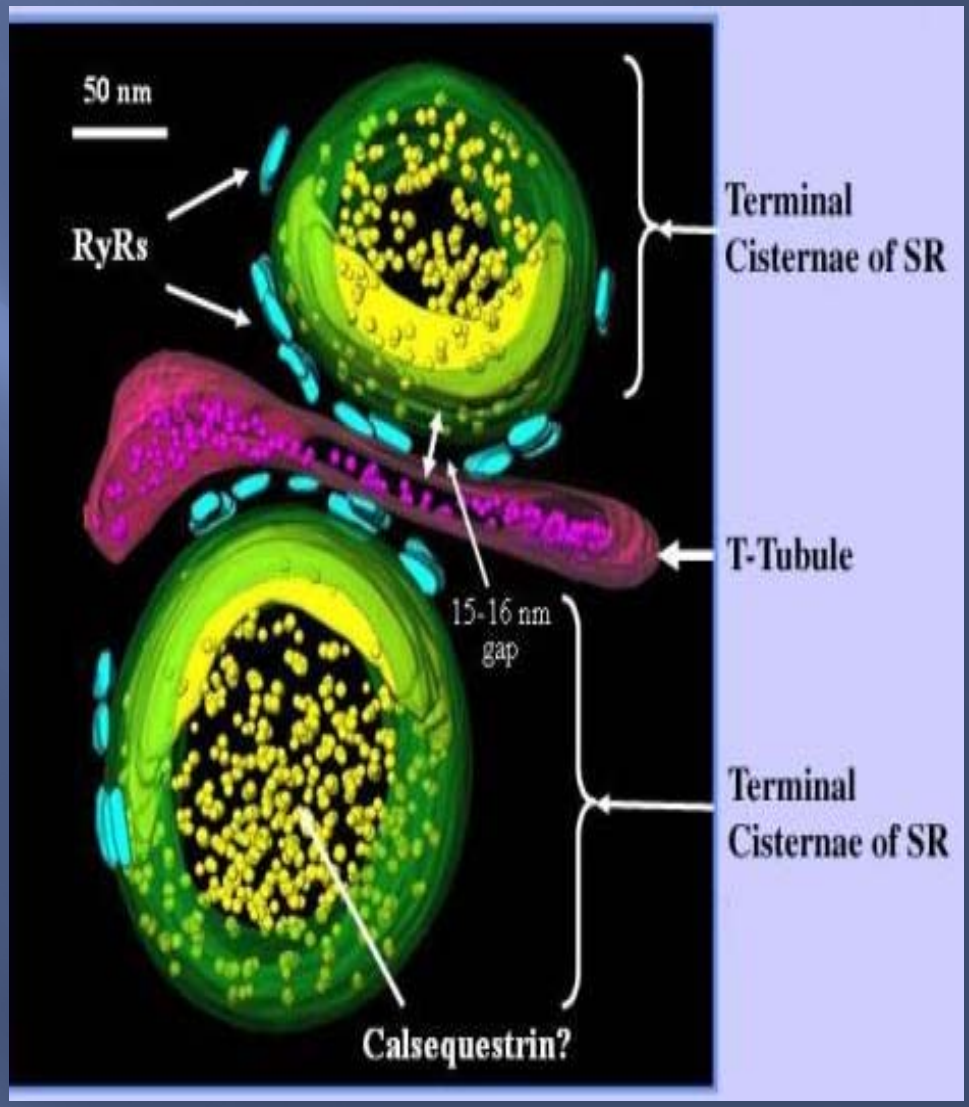
- A pharmaco-environ-genetic disorder

-Electron tomography & electron crystallography
-Reconstructed “views”

Ryanodine receptor:
Channel regulating calcium

Protein
Product of 3 genes
- **Skeletal & heart muscle**
- **Stomach**
- **Endothelium**
- **Brain**

Defect→
Arrhythmogenic dysplasia
Cardiomyopathy
MH

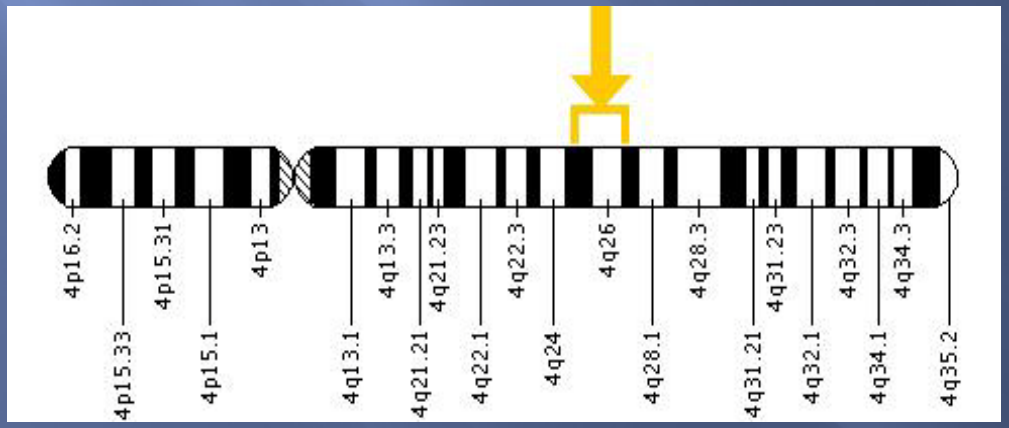


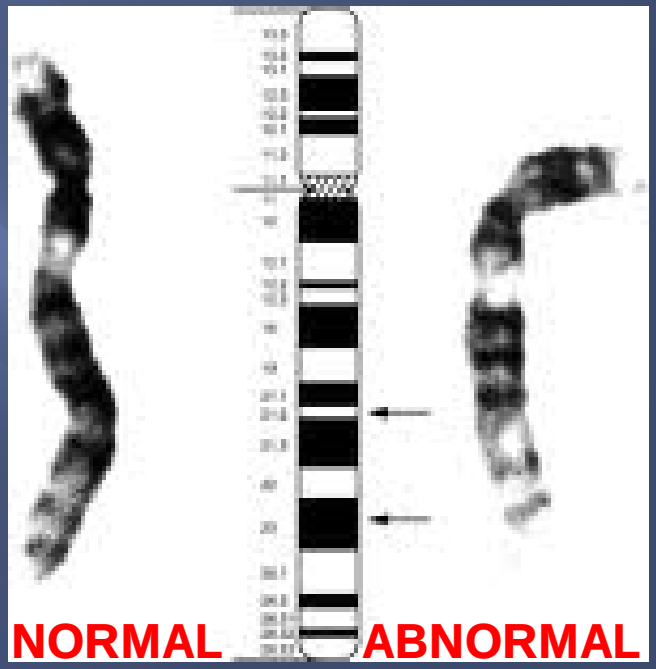
Atrial fibrillation after CABG (chromosome 4q25 region)

Long QT syndrome

Who may / may not benefit from β adrenergic blockade

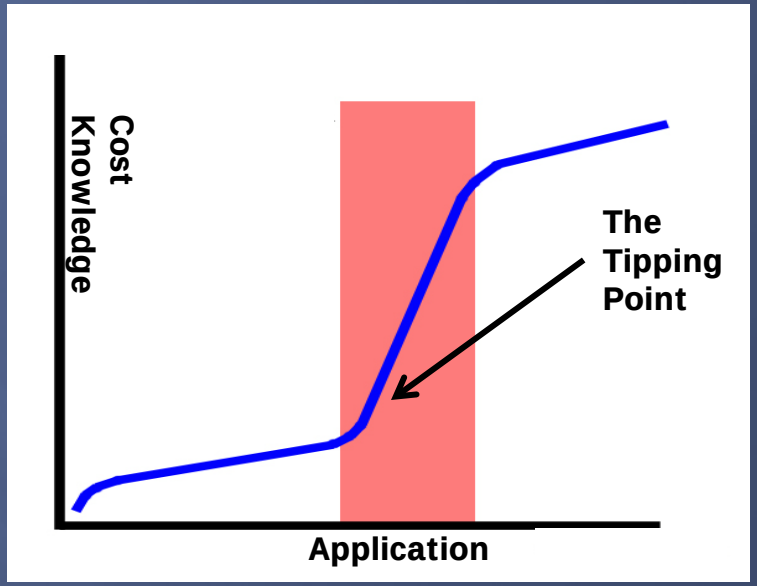
4q25 region





Ideogram

From Gene to Cure?



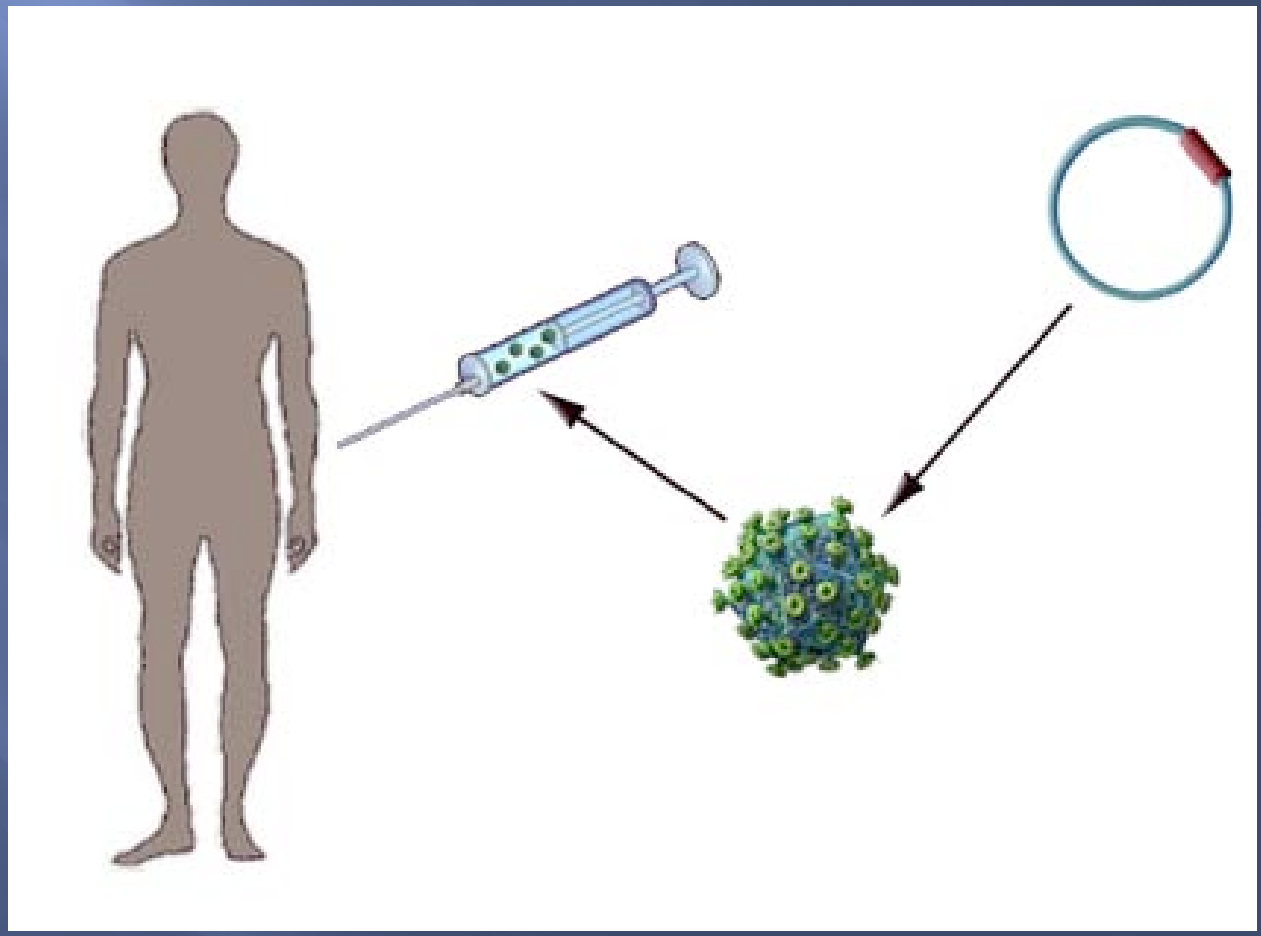
- Genetic medicine is at the tipping point
- The pace of medical research/progress is not linear

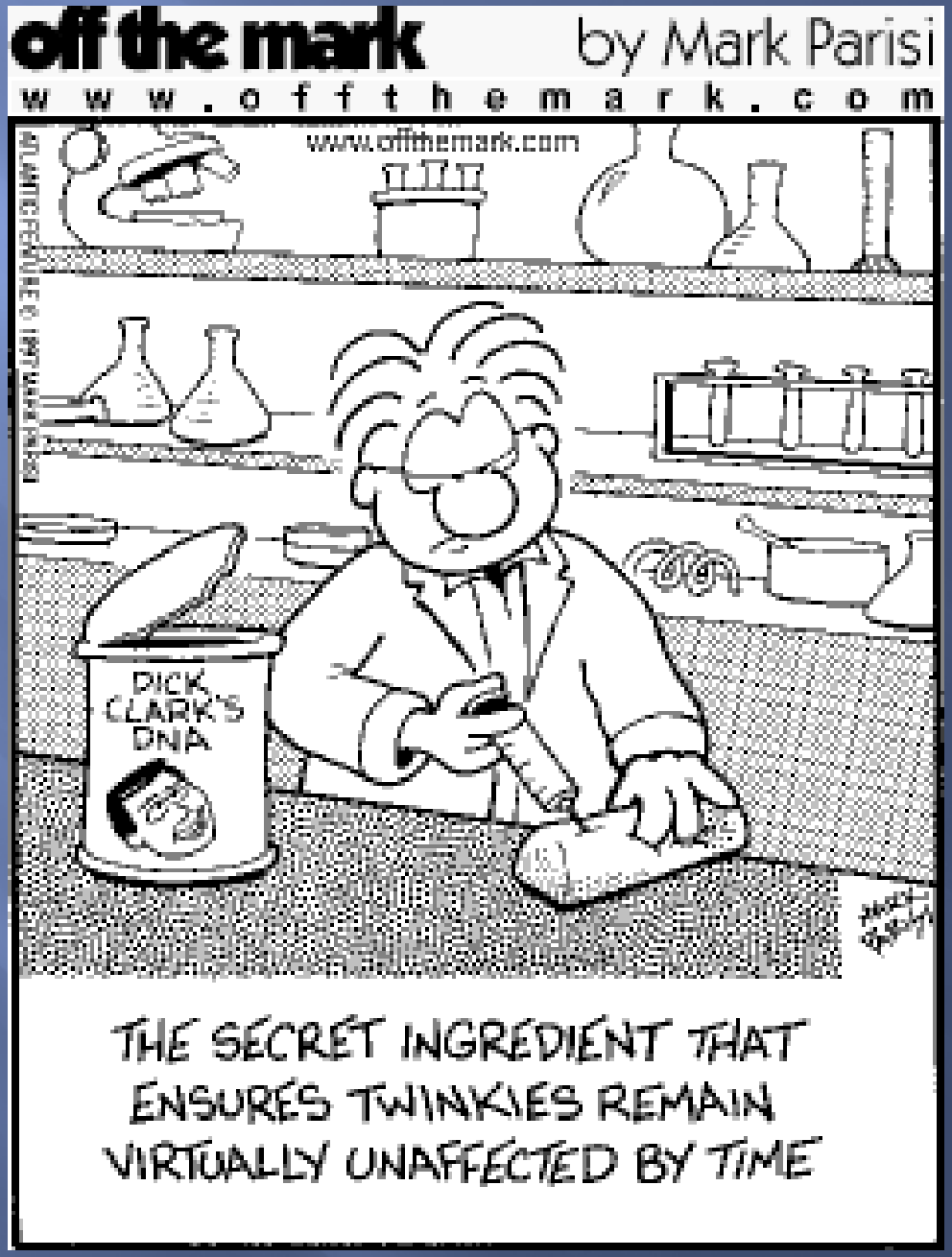
- 50 years slow progress ≠ continued slow progress!

- Great progress with SSD
- Insert normal Hgb gene into bone marrow
- Drugs that block sickling

In vivo gene therapy

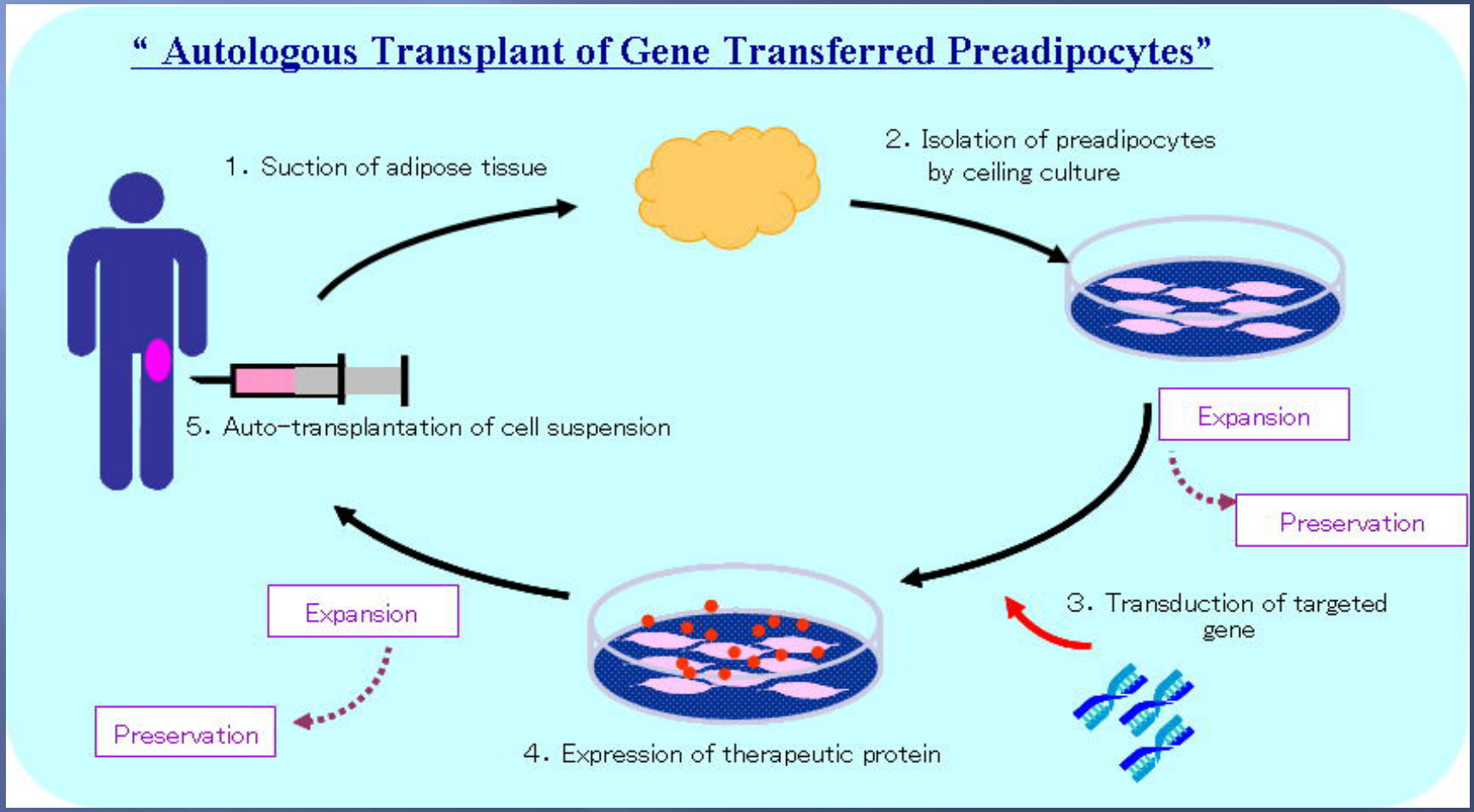
Therapeutic DNA is injected directly into the body cells via one of two types of viruses




off the mark
by Mark Parisi
www.offthemark.com
www.offthemark.com
DICK CLARK'S DNA
THE SECRET INGREDIENT THAT ENSURES TWINKIES REMAIN VIRTUALLY UNAFFECTED BY TIME

Ex vivo gene therapy

Remove cells from body, add the specific DNA, return them to the patient



Statistical

- If toxic or failed response is 1:1000, then doing a study that enrolls 20K treated will identify only 20

- We do not have a functional mass reporting system

Economical

- Expensive
- Rx companies not motivated to reduce market size

Regulatory

- FDA cool to require genetic testing

Providers

- Data & tests exist, evidence-based use lacking

Logistical

- Current infrastructure inadequate
- Testing largely done in centralized labs
- Shipping / time delay dissuades use

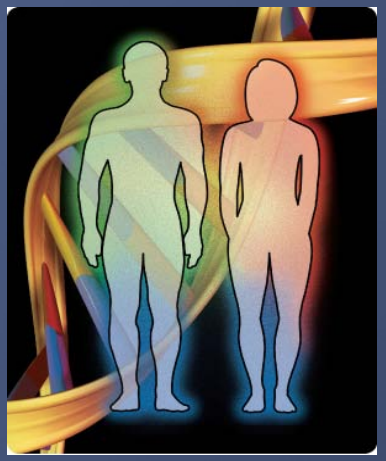
Ethical

- “leave mother nature alone”
- Religious objections
- “not always good to know”
- Create genetic “under-class”

A look to the future

- Cost will decrease
- Testing will be widely available
- Knowledge will fuel interventions
- Interventions will improve outcome
- Primary care → “genetic medicine”
- Ban on genetic discrimination
- Great controversy will continue!

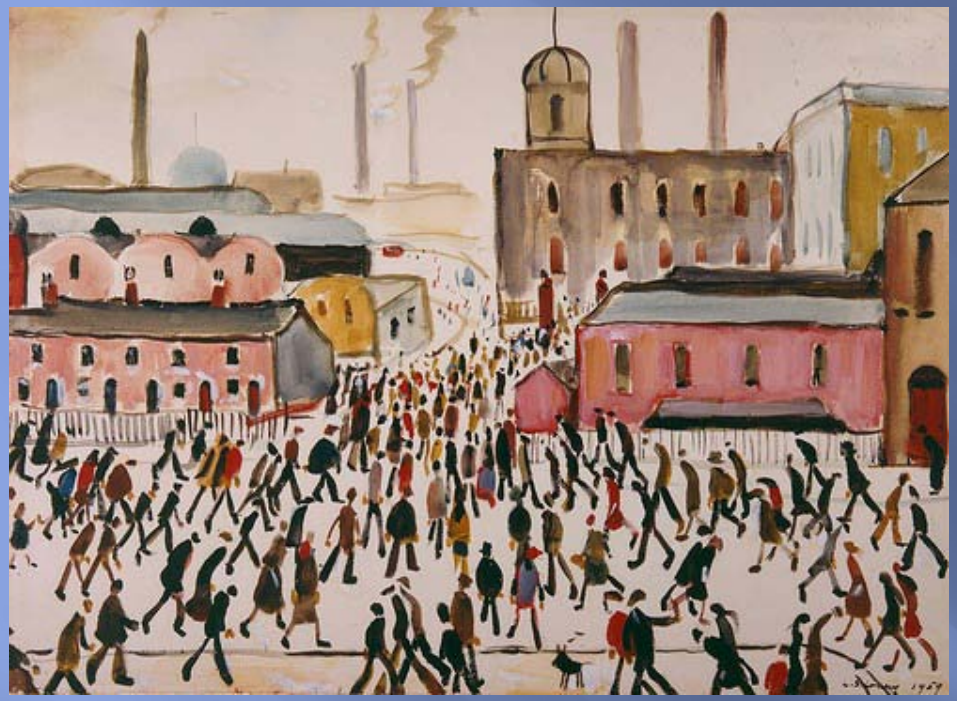
Era of *personalized medicine*



- Approach to care based on the individual
- Consider age, comorbidity, personal preferences
- Individual genomic information in Rx selection

Selected Genomic Biomarkers

Biomarker	Disease	Drug
C-kit	GI stromal tumor	Imatinib mesylate
CCRS	HIV	Maraviroc
P-450 variants	Many disorders	Warfarin, voriconazole
EGFR	Non small cell lung CA	Erlotinib
HER2	Breast CA	Trastuzumab



LS Lowry
English
1887-1976

The Matchstick Men