SOME PERSPECTIVES ON EVALUATING THE RISK OF MEDICAL PRODUCTS

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THE NATION LOS ANGELES TIMES ★ TUESDAY, JULY 12, 2005 A19

For Some Parkinson's Drugs, the Side Effect May Be Gambling

Common prescriptions for the disease are linked to heavy betting in rare cases, a study shows.

C4 WEDNESDAY, NOVEMBER 1, 2000

Family Almanac

Vaccine-Mercury-Autism Connection?

Los Angeles Times

FRIDAY, APRIL 8, 2005

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Antidepressants Called Unsafe For Children

4 Medications Singled Out In Analysis of Many Studies

FDA Warns on Painkillers; Drug Pulled

Reactions and Recalls

The Washington Post

VA

SATURDAY, DECEMBER 18, 2004

Celebrex Trial Halted After Finding Of Heart Risk

THURSDAY, NOVEMBER 18, 2004 A17

Campaign Waged Against Crestor

Group Calls Drug Unsafe

The New York Times

opyright © The New York Times NEW YORK, MONDAY, 2

Two Portraits Lay Firebombing of Subway To 'Twisted' Rage or the Effects of Prozac

SCIENCE AND HEALTH THE WASHINGTON POST

Arthritis Drug Study in 2000 Found Risks

Results Show Pfizer May Have Known About Celebrex's Heart and Stroke Problems

BEFORE VIOXX…

- Triazolam (Halcion™) and neurological disturbances, 1980's
- Fen-phen and pulmonary hypertension/heart valve damage, 1997
- Troglitazone (Rezulin™ and liver damage, 1999
- Isotretinoin (Accutane™) and suicidality, 2000
- Alosetron (Lotronex™) and intestinal damage, 2000

AND VACCINES…BLAMED FOR

- SIDS
- Brain damage
- Seizure disorder
- Diabetes
- Multiple sclerosis
- Autism
- Arthritis
- Gulf War Syndrome
- ADD

TRUTH AND TRUISMS ABOUT PRODUCT SAFETY

- All effective products have some risk
- Rare risks may not be identified during product development
- Level of acceptable risk depends on level and type of benefit
- What is "acceptable risk" differs among individuals
- If it happens to you the risk is 100%

POLICY ISSUES

- How much information about a drug's safety should be obtained prior to marketing?
- How much of this information should come from randomized controlled trials?
- What level of resources should go to tracking potential new safety problems after marketing?
- What level and type of information should generate public alerts?

MANY NEW PRODUCTS

- Breakthrough treatments
  - Rheumatoid arthritis
  - Gastro-esophageal reflux disorder (GERD)
  - Osteoporosis
  - AIDS

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- Newly treatable common conditions
  - hyperactivity
  - hair loss
  - Pre-menstrual syndrome

POPULATION SHIFT

- Baby boomers started turning 50
- Elderly population rapidly increasing
- Increased medical needs…availability of new products means
  - more people being treated
  - more people taking multiple medications
  - more people experiencing side effects
  - more drug-drug interactions

CHANGING RISK PERCEPTIONS

- Studies reporting large numbers of fatal adverse drug events each year
- Reports on medical errors
- Highly publicized product withdrawals
- Alternative/complementary medicine
- Internet (information and mis-information)

FINDING NEW RISKS: TWO COMPONENTS

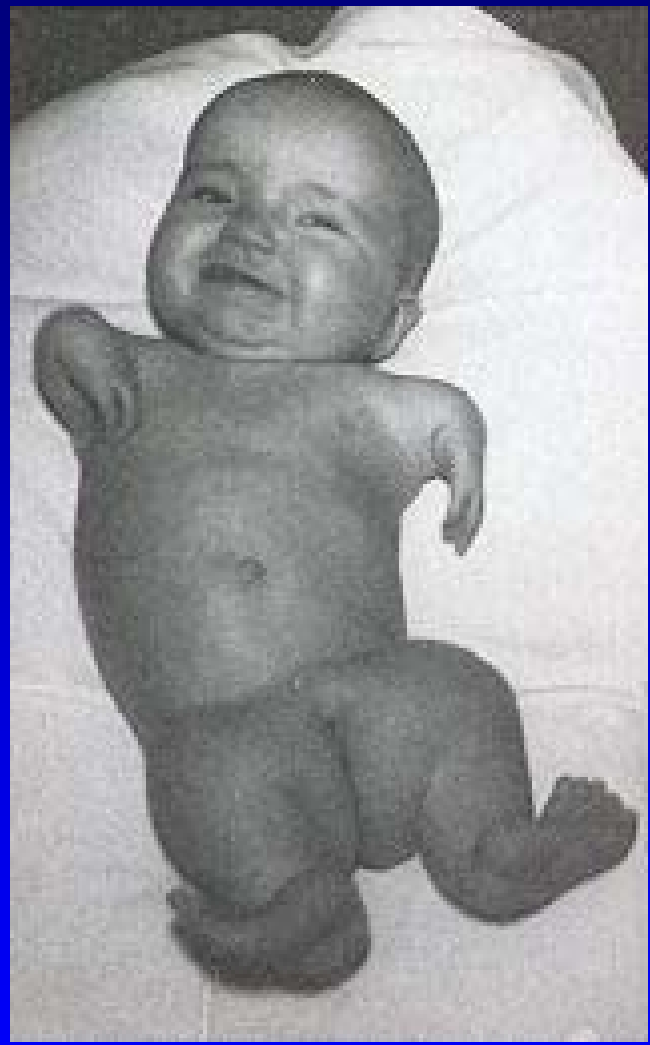
- Signal generation
  - Monitoring of "spontaneous reporting systems"
  - Monitoring health care databases
- Signal confirmation
  - Conducting further prospective studies to better quantify risks
  - Conducting observational studies to assess possible rare risks

SPONTANEOUS REPORTING SYSTEMS (SRS)

- The worst type of data base imaginable
  - Voluntary reporting based on suspicion that drug may have caused event; usually no evidence except temporal association that drug caused event (NO NUMERATOR)
  - Don't know how many took drug (NO DENOMINATOR)
  - No quality control—all reports submitted get put in data base "as is"

MONITORING A SRS

- Some serious events are almost always the result of drug exposure. For these, temporal association alone is highly suggestive or even definitive
  - Anaphylactic reaction within seconds or minutes of exposure
  - Aplastic anemia
  - Sudden liver or kidney failure
  - Q-T interval prolongation



MONITORING A SRS

- For serious events that occur in background, independent of medication use, more difficult
  - Suicide and suicide ideation
  - Emergence of autoimmune disease (MS, lupus)
  - Myocardial infarction
  - Stroke
  - Cataract formation

WHAT TO DO WITH A SIGNAL?

- If action is late, more people may be harmed if there is a real problem
- If action is early, people may stop taking medications unnecessarily if no real problem
- False signals lead to unwarranted public concerns and can have major financial consequences for manufacturers
  - Bendectin for morning sickness
  - Silicone breast implants

STATISTICAL APPROACHES TO SRS MONITORING

- Some early papers
  - DJ Finney, 1960's-70's
- Application of methods developed for industrial quality control, 1980's-90's
  - Shewhart's control charts
  - Cumulative sum (CUSUM)
- Data mining, 1990's-2000's

D.J. FINNEY

- Worked with WHO in 1960's to establish international drug monitoring programs
- Papers focused on general monitoring strategies and practical issues rather than statistical methods
  - Use of precise terminology
  - Systematic recording of data
  - Regular tabulation by time period, demographic characteristics, geographical location, etc.

CONTROL CHART METHODOLOGY

- Basic concept: detect deviation from established pattern
- Could be useful to detect
  - Problems resulting from change in manufacturing process
  - Contamination or other problem with lot-based production of biologics
  - Seasonal effects
  - Interaction with newly available drug
- Less relevant for rapid identification of problem with new drug

DATA MINING

- DuMouchel: Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system, *American Statistician*, 1999 (with commentaries)
- Innovative step in automated signaling of potential problems

SIMPLE IDEA

- Construct contingency table where rows represent drugs in use and columns represent reported types of events
- Table will be sparse!
- Analyze table to see if some events are more frequently associated with certain drugs
- Use Empirical Bayes methods to shrink estimates, reduce impact of large relative risks based on very small numbers

IMPLEMENTATION COMPLEX

- Many drug-event associations will be artifactual
  - Events more common in older populations will be more frequently associated with drugs given to older people
  - If unsafe medication is commonly given to people also receiving a safe medication, the latter will also be associated with events
- Can account for some known confounding issues in the signal-generating algorithm

HEALTH CARE DATABASES

- Claims databases maintained by HMOs and government programs (Medicaid) can provide information about drug risks
- Could be used both for signaling and for confirming signals seen in a SRS
- Advantages
  - Data already collected for financial purposes
  - Definable numerators and denominators
- Disadvantages
  - Medical information often quite limited
  - Little information on outpatient events
  - Deaths outside hospital not likely in database
  - Studies can usually not be conducted quickly

HEALTH CARE DATABASES (2)

- General Practice Research Database
  - Data from 400 UK medical practices
  - Established 1987; managed by UK regulatory authority
  - about 3 million patients currently followed
- Information specifically collected for public health research purposes
- Increasingly used to study drug AEs

PROSPECTIVE POST-MARKETING STUDIES

- Companies sometimes agree to conduct further studies as part of drug approval negotiations
- These may be randomized studies; more often, observational studies
  - Incidence of adverse effects
  - Outcomes in specific subgroups inadequately studied in pre-market trials
- Difficult to control for confounding variables in observational studies

OBSERVATIONAL DATA

- Good for estimating incidence, identifying dramatically increased risk
- Not so good for identifying modest-to-moderate increase in risk
- Many cases of 2-3 fold risks of widely used products not identified until large randomized trial was done
  - Cardiac Arrhythmia Suppression Trial (CAST)
  - Women's Health Initiative
  - Cox-2 inhibitors

STATISTICS AND POST-MARKETING SURVEILLANCE

- Relatively little attention given by statisticians to this area
  - Until recently, minimally visible
  - No one giving grants to support such research
  - Interest focused in small groups at FDA and in drug companies

VACCINE SAFETY:
SOME SPECIAL ISSUES

MONITORING VACCINE SAFETY

- A number of factors affect public risk perception for vaccines
  - Target population is healthy
  - Target populations often most vulnerable: babies and elderly
  - Vaccine-preventable diseases barely visible anymore; reduced perception of vaccine benefit
  - Vaccinations are often mandatory

MONITORING VACCINE SAFETY (2)

- Post-marketing safety surveillance is especially difficult for vaccines
  - target populations (babies, elderly) often at elevated risk for certain serious events; coincidental temporal associations expected
  - universality of use precludes finding appropriate control groups
  - assessing causality very problematic
  - media attention stimulates reporting

VACCINE-INDUCED VS. COINCIDENTAL EVENTS: AN EXAMPLE

- Four million births in the U.S. every year
- Current vaccination schedules call for multiple administrations of 6 different vaccines, starting at birth, and at 2,4,6, and 12-15 months of age
- Sudden Infant Death Syndrome (SIDS) occurs (during the first year of life) at a rate of about 1/1800 in the U.S.
- Each year, 50-70 children can be expected to die of SIDS by chance within 2 days of being vaccinated

VACCINE LICENSURE

- Vaccines for common diseases can be evaluated for efficacy in relatively small studies
- Studies are generally of short duration—typical followup is one month post final vaccination
- Studies are unable to rule out substantial increases in serious events

STUDY SIZES IN RECENT VACCINE DEVELOPMENT PROGRAMS

VACCINE	SIZE OF CONTROLLED STUDIES	TOTAL VACCINEES PRE-LICENSURE	POSTLICENSURE COMMITMENT
Varicella	956	11,102	90,000
Rotavirus (1)	2558	11,463	20,000
Pneumococcal	38,000	19,000	60,000
Rotavirus (2)	70,000	?	?

POWER TO DETECT INCREASED EVENT RATE

Sample size	5%-10%	1%-2%	0.1%-0.2%
1000	0.82	0.17	0.05
5000	0.99+	0.80	0.07
10,000	0.99+	0.98+	0.17
50,000	0.99+	0.99+	0.79

OPTIONS FOR IMPROVING SAFETY MONITORING

ACTIVE SURVEILLANCE

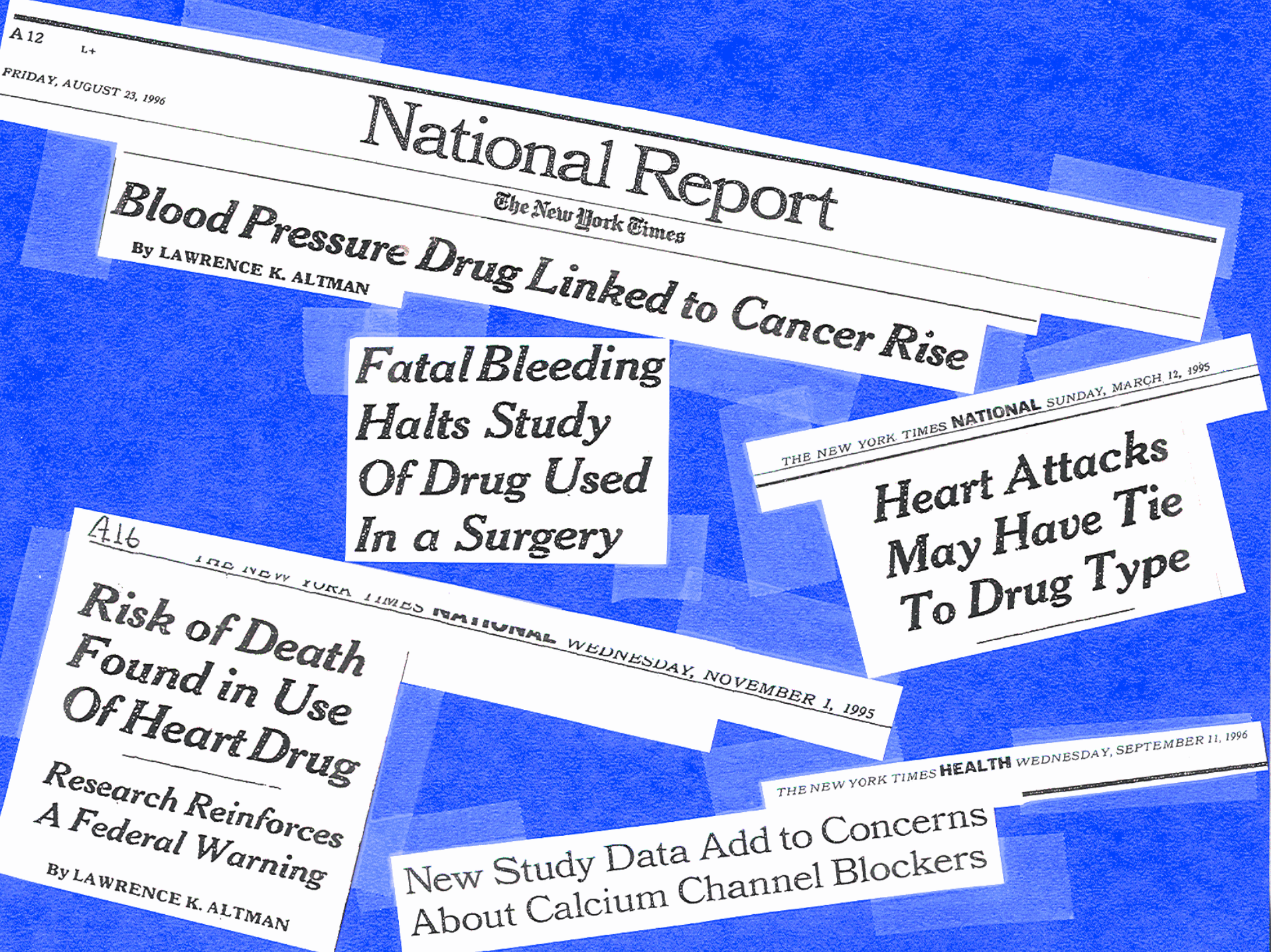
- Prospective followup of defined cohort: observational study
- "Sentinel" centers
- Provide response cards with first (number) of prescriptions
- Provide product only via a registry that collects data on all recipients

IMPROVED UTILIZATION OF CLAIMS DATABASES

- Develop better statistical tools for monitoring data, detecting signals
- Enhance data available electronically to facilitate rapid study

THE ROLE OF CLINICAL TRIALS

- Observational approaches unlikely to detect sub-dramatic but important increases in common adverse events
- For products expected to be widely used in fundamentally healthy populations, perhaps should consider expanded trials with safety as primary or co-primary outcome
  - Pre-marketing?
  - Post-marketing?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FRIDAY, AUGUST 23, 1996
National Report
The New York Times
Blood Pressure Drug Linked to Cancer Rise
By LAWRENCE K. ALTMAN
Fatal Bleeding Halts Study Of Drug Used In a Surgery
THE NEW YORK TIMES NATIONAL SUNDAY, MARCH 12, 1995
Heart Attacks May Have Tie To Drug Type
A16
THE NEW YORK TIMES NATIONAL WEDNESDAY, NOVEMBER 1, 1995
Risk of Death Found in Use Of Heart Drug
Research Reinforces A Federal Warning
By LAWRENCE K. ALTMAN
THE NEW YORK TIMES HEALTH WEDNESDAY, SEPTEMBER 11, 1996
New Study Data Add to Concerns About Calcium Channel Blockers

CALCIUM CHANNEL BLOCKERS

- Commonly used medications in coronary artery disease
- Epidemiological studies suggested these products were associated with higher risk of death
- Large randomized trial showed no difference in risk between these and other products used for same indication

INCREASED COSTS

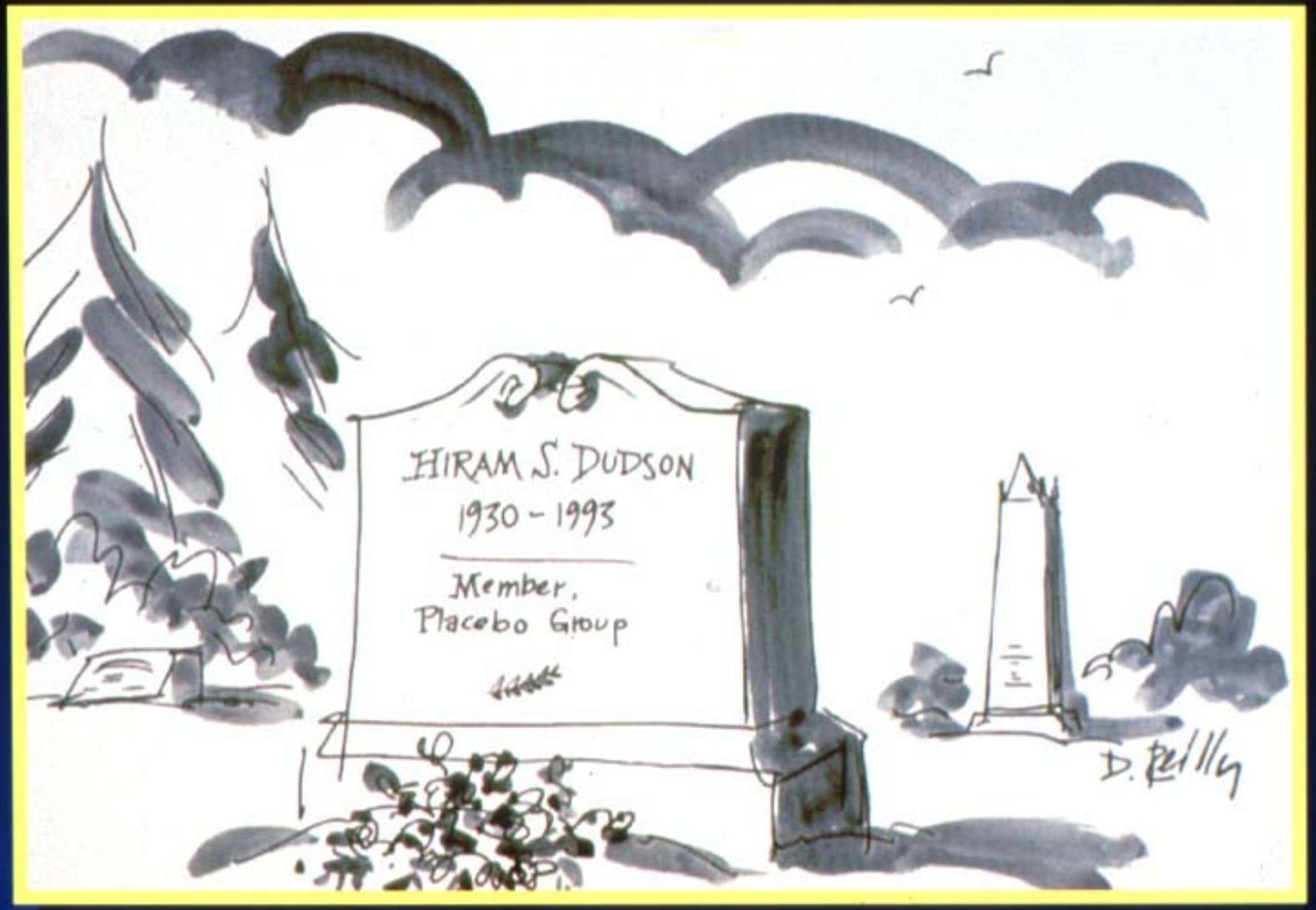
- Who will pay for
  - Modifying claims databases to include more data
  - Statistical research into signaling methods for available databases
  - Sentinel centers
  - Patient registries
  - More and/or larger clinical trials

COST CONSIDERATIONS

- Most proposed system changes will come at a price
  - More federal resources for FDA will mean fewer resources for something else, or higher taxes
  - More drug company expenditures for larger and/or more studies will mean higher prices, possibly fewer drugs
  - More concern about safety may mean longer delays to approval of new drugs
- Some fear return to more cautious approach of 1970's-1980's

HOW SHOULD WE BALANCE BENEFIT AND RISK?

- Answer may depend on where you sit
  - Your child has a serious illness for which current treatments either don't exist or are unsatisfactory
  - Your spouse died of a stroke shortly after starting a new medication
  - You need multiple drugs and want them to be safe, but worry that if costs go up you won't be able to afford them


HIRAM S. DUDSON
1930 - 1993
Member,
Placebo Group
D. Reilly


THE WIZARD OF ID PARKER & HART
WOULD YOU LIKE TO VOLUNTEER TO TEST A NEW MEDICATION?
9-11
ONLY IF I GET THE PLACEBO

CONCLUDING REMARKS

- Monitoring drug safety is a highly complex task
- Improvements are needed in automated signal detection
- Improvements are needed in ability to rapidly do follow-up studies to confirm or refute signals
- Need to confront important policy issues relating to the extent and reliability of safety data that should be collected for widely used products