Class NINE – Innovation organization Issues in the Life Science Innovation System

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"Innovation Systems for Science, Technology, Mfg. Energy and Health"

PART ONE:

The Life Science R&D Model:

The National Institutes of Health (NIH)

NIH Historical Backdrop

Remember the historical context:

- Pre-WW2 and WW2 – modest lab attached to Public Health Service
- Post-WW2 – FDR and Vannever Bush propose "War on Disease" – saw what happened with Penicillin – disease death rate for soldiers in WW1 – 16/1000; WW2 – down to 0.4/1000
- V.Bush launches Basic Research model and "one tent" with R&D focused at NSF
- Truman vetoes NSF, not stood up 'till '50
- So: Science agencies proliferate - "National Institute of Health"
- But NIH is unadorned Basic Research model
- No agency or research connectedness – no cross-agency or cross-discipline R&D
- Disease groups and Congress: separate institutes with separate research paths

RESULT: Dr. Anthony Fauci, Director of NIH's NIAID, writes:

"The path to product development has not been a part of [NIAID's] research strategy"

-- Nature, 421:787 (2003)

What NIH/Biotechs got Right:

- NIH Trained everybody – grad students educated by mentor based education – funded with on R&D spending – NIH has seen to that
- This knowledge base has spawned entrepreneurial biotechs – these co's are huge US innovation opportunity
- Biotechs can get venture capital and even IPO's 10 to 15 years or more before products enter market – incredible to get long term early stage development funding

What NIH/Biotechs Got Right, Con't

- Key to this is value of IP – can command monopoly rents for 20 yrs. minus FDA trials
  - FDA certification/tech validation role – unique in technology field
  - FDA OK unique – assures market entry
  - patents not as valuable in physical science: more routes to solutions, no rigorous FDA trials with success certification
- Eliminated "upstairs-downstairs" attitudes between academics and industry – movement back and forth – prof's on bio bds. – foundation there for connected science -- this arrogance problem still plagues physical science
- NIH support base has put $30+/-B/year into R&D – staggering success

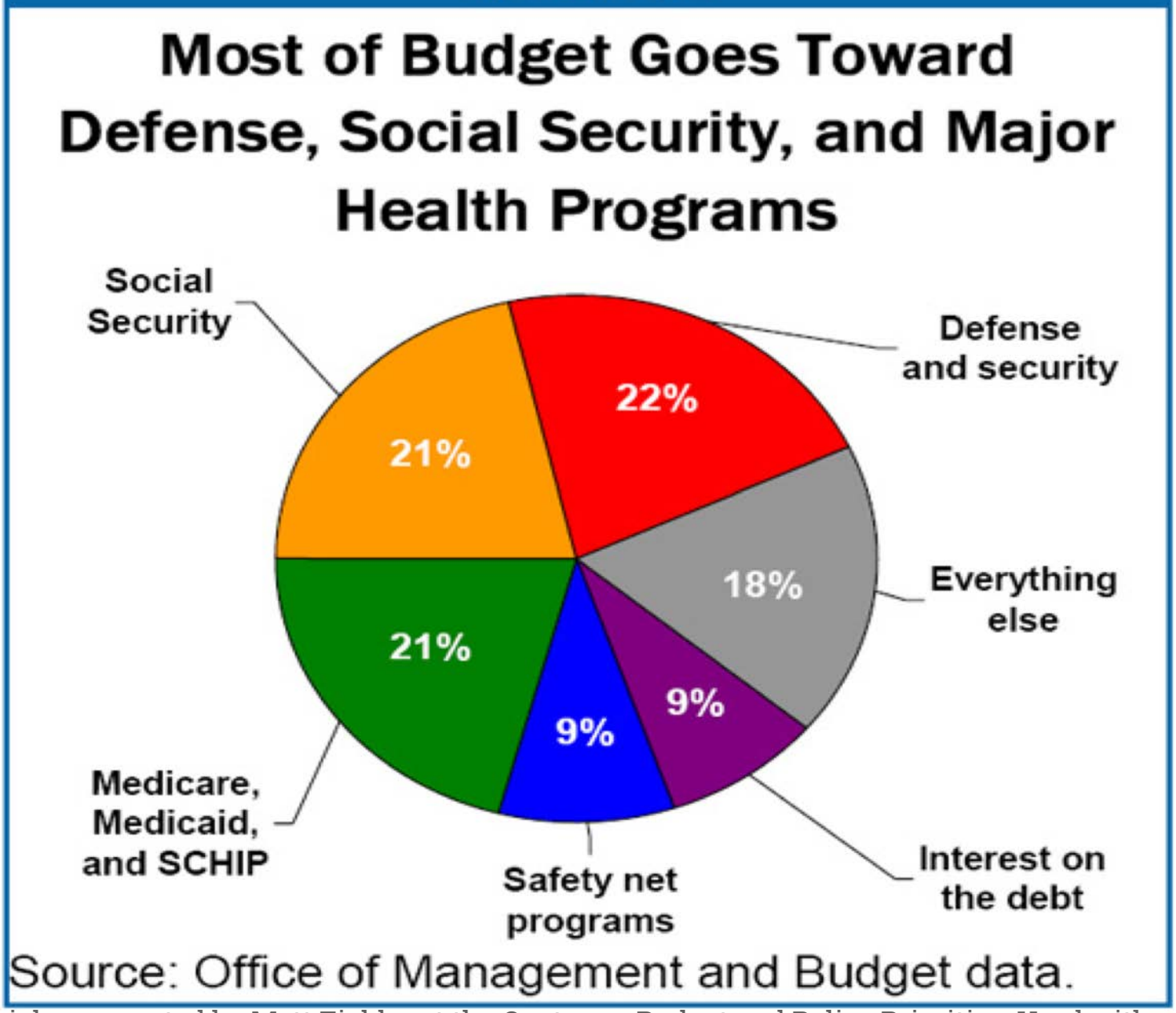
But: Oncoming Innovation *Trainwreck*:

- Economic model for biotechs/pharmas requires blockbuster-sized markets
- This model leaves out:
  - Most 3rd World disease
  - Infectious disease
  - Small population diseases
  - Remedies that serve smaller than target population market taken off market
  - Some argue that 90% of world medical R&D spent on 10% of diseases
- No sign yet of personalized ("or precision")/genome based medicine and no economic model for it
  - "Big Data" effort at FDA – no funding
- Litigation threat makes firms risk adverse

Oncoming Cost *Trainwreck*

- Gov't share of US health market will be 50% around 2020 – "socialist" sector?
- Health care spending by 2025 may account for 9% of GDP – not manageable – taxes as % of GDP 16-19% - will crowd out all gov't
- Health Care spending per person may reach over $11,000/yr. (2005: $6040)
- Medicare prescription drug spending $4.5B in '04, $6.9B in '06 – growing with demographics
- GAO: by 2040 federal revenues (if tax cuts extended) will only pay for interest on debt – no Medicare, no Soc Sec, no defense, no gov't
- Gov't unprepared for demographics

Re: Shorter Term Effects:



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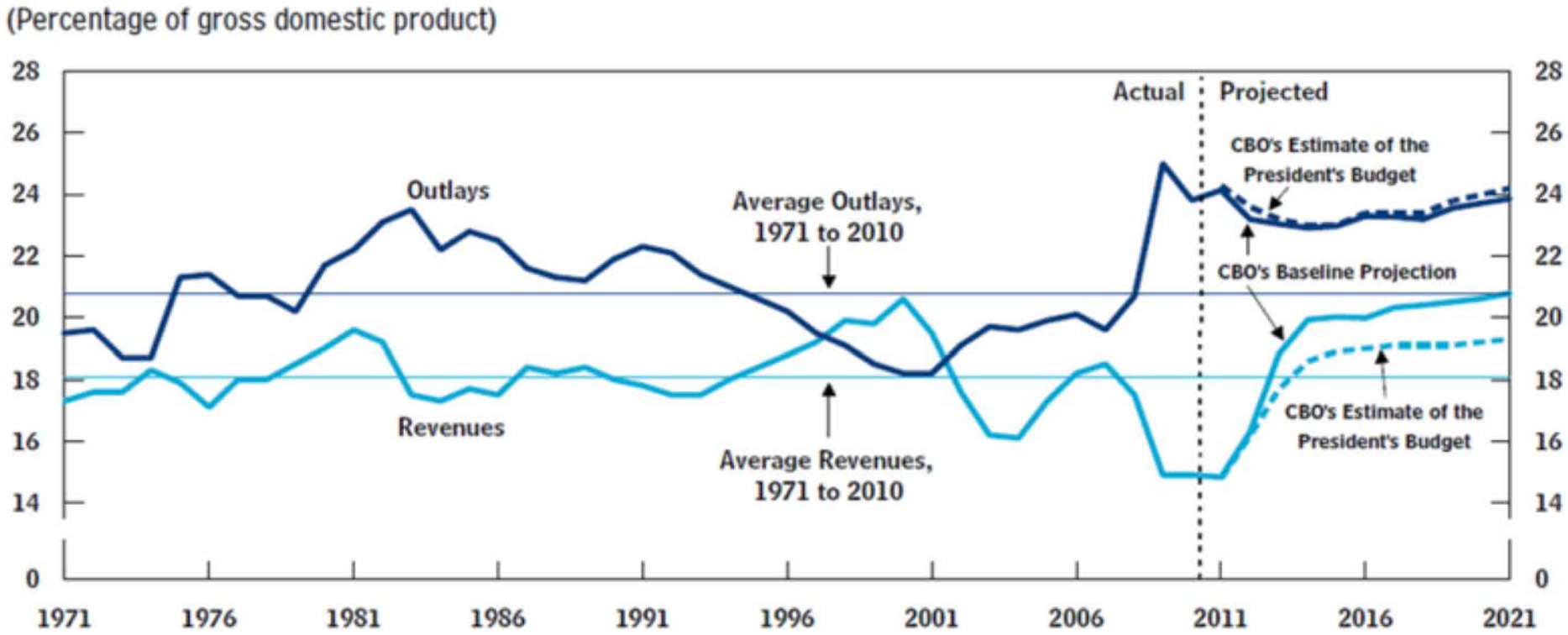
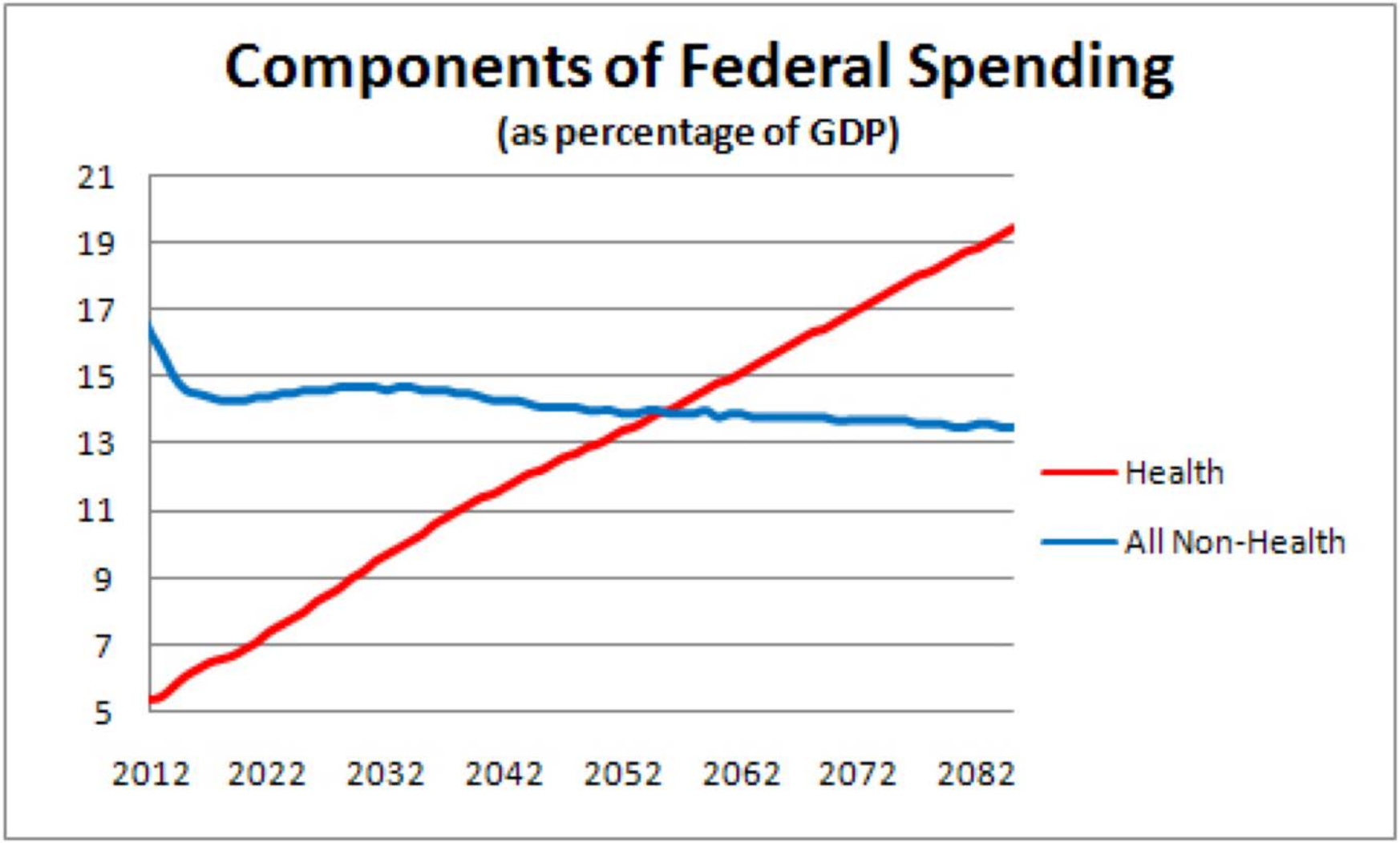
CBO – Revenues and Outlays as % GDP

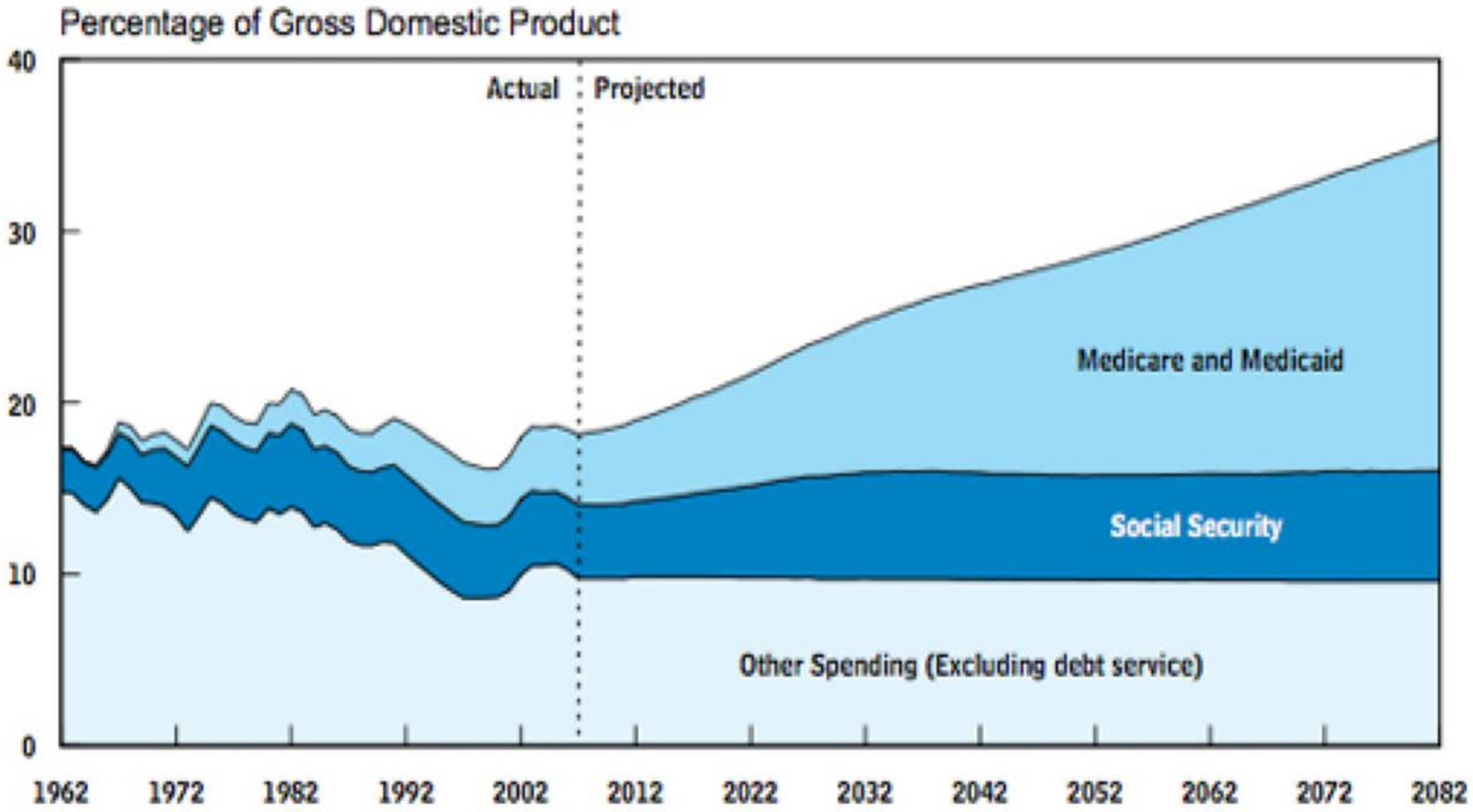


Source: CBO – Analysis of the President's Budgetary Proposals for 2012

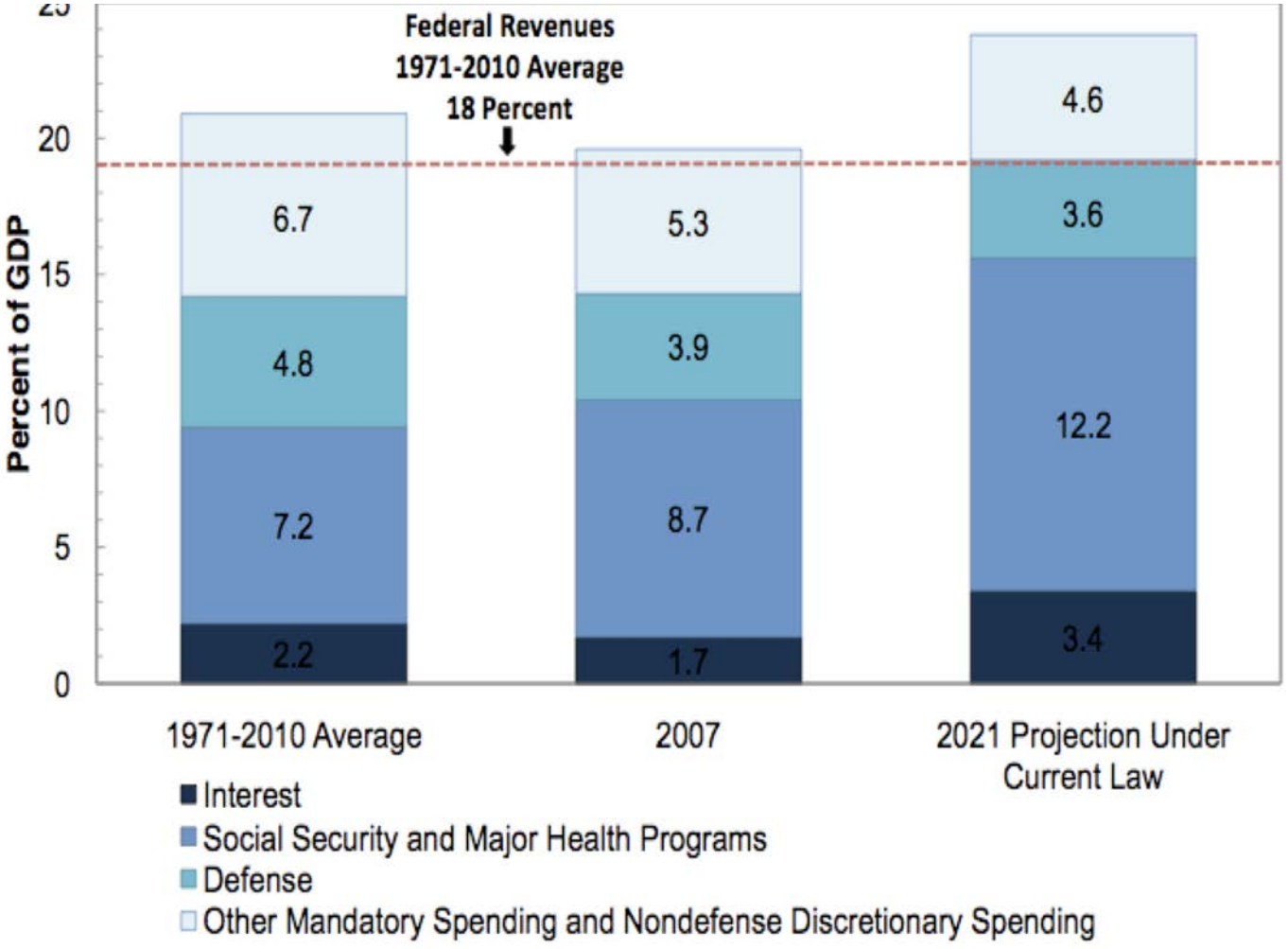
Longer Term: Dominance of Health as a Future Factor in Federal Spending



Projected Federal Spending Over the Longer Term – Role of Entitlements



Longer Term - Elements of Fed Spending:



National Institute of Medicine (NAS), Enhancing the Vitality of the NIH (2003)[now: Acad. of Medicine]

- 27 Institutes and Centers at NIH – Stovepipes?
- NIH Ex-Dir. Harold Varmus 2001: – NIH would be more efficient and more manageable if far smaller number of larger institutes, organized around broad science areas
- Other side of the argument: no. of IC's allows problem focus

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

IOM – NIH Underlying issues:

- NIH Budget doubled from 1998-2003 to $28B
  - FY16: $32B
- Demographics changing, patterns of illness changing, biothreats possible
- NIH too fragmented?
- Unable to respond quickly enough?
- Unable to manage fundamental new science challenges?
- Is the proliferation of new entities the answer or the problem?
- Should NIH add on more or manage?

IOM – NIH Underlying Issues

- IOM - for now, focus on capabilities at NIH not nos. of boxes
- Report says: NIH is "not only imperfect", nobody would have ever designed NIH this way at the outset
- Focus on modifications that focus on enhancing NIH's ability to pursue "time limited strategic objectives that cut across all institutes"
- NIH needs special ability to pursue high-risk, high-return projects

IOM – NIH Underlying Issues

- Current NIH capabilities –
  - Decentralized structure
  - Many set R&D priorities
  - Benefits to investigator-initiated grants
  - Fundamental research
  - Competitive peer review system for grants
- But: changes on the science frontier, new health concerns

IOM Recommendations:

- Centralize management – too many layers
  - More authority for NIH Director, increased responsiveness, greater flexibility, opportunity for coordination
- Force justifications for adding any more boxes – unmanageable
- Strengthen clinical research via public private partnerships & new center for this
- Strategic Planning across stovepipes
  - For: Cross-cutting initiatives

IOM Recommendations, Con't:

- Cross-NIH budgeting for cross-cutting efforts with 10% of budget based on Strategic Plans
  - Reconsider plans every two years
  - Multi-year, time-limited
  - Add'l staff for Direcctor to jump-start these
- Strengthen NIH Director – to control Strategic Planning and Trans-agency initiatives
  - Create add'l operations staff and capability for Director

IOM Recommendations, Con't:

- Create an NIH DARPA –
  - Director's "Special Projects Program"
  - For: high-risk, exceptionally innovative, high-payoff projects
  - $1b/year
  - Rapid review and initiation of promising projects
  - Special extramural panels available to advise
  - Program Director reports to NIH Director
  - Project not peer review based

IOM Recommendations, Con't:

- Shape up the NIH intramural program – program metrics and accountability
- Standardize data and info systems – IC's and researchers can't draw on each other's databases, no common metrics
- Limit terms of NIH & IC Directors and set powers, require annual reviews

IOM Recommendations, Con't:

- Limit authority of Nat'l Cancer Institute – now separate, fit it within NIH

- Retain integrity, quality of appt's to Advisory Comm's – reform across NIH

- Better funding for research management

MY COMMENTS ON IOM RECOMMENDATIONS:

MAJOR NIH ORGANIZATIONAL PROBLEMS:

- NIH not a "connected" organization, doesn't support connected research
- Very hard to stand-up larger scale "Grand Challenge" Model approaches across NIH
- Cannot set initiatives across stovepipes
  - almost no cross agency work (except Director Elias Zerhouni's "Roadmap"/Common Fund)
  - Almost no coordination with outside agencies like Army Med Res, DARPA, DHS' HSARPA, little w/FDA
- Primarily small grant research – but science advance doesn't necessarily come from small grants

NIH Problems, Con't

- Slow-moving – grant approvals can take a year or more – can't respond to emerging problems quickly
  - -ex., biothreats, new infectious diseases
- Peer review tends to avoid high-risk, high-payoff approaches
  - Conservative – missed SC's, genome, and Venter's automated genome processing
- Focus on basic-only R&D works only if profound connection to industry – but that isn't there
  - Weak tech transition office
  - Biotech's, Pharmas focused on blockbuster markets – some say only 10% of health R&D aimed at 90% of world disease problems

NIH Problems, Con't:

- NIH not organized for cross-disciplinary R&D
  - Advances will come from areas between disciplines – ex., biotech
  - Physical science funding in decline
  - NIH will suffer from this decline, too – will limit life science advance
- NIH not organized to develop next generation of research tools – also critical to FDA
  - Benefited from simulation and modeling, but no work to develop next generation
- Weak NIH Director can't set goals, manage 27 mixed-performance IC's

NIH Problems, Con't:

- Can't tackle major new science opportunity areas
  - Nanotechnology – health is early winner but of $1.3b gov't program, only $160 in '07 from NIH – still a problem
  - Drug-only focus of research omits huge fields – bioengineering (devices) center –NIBIB-stood up but underfunded (only $300m/year)
  - Bioinfomatics still weak
  - Collins: NCATS for "translational" research being created but how will it connect to industry?

So: IOM's '03 Report Only Captures Part of NIH's Problems

Robert M. Cook-Deegan, "Does NIH Need a DARPA?", (Issues in Sci.& Tech, Nat' l Aca. Magazine, Winter 1996)

M.D., Prof. of Medicine,
Duke's Genome Institute

Cook-Deegan: The DARPA Culture:

- Expert staff, focused mission
- Lean management
- Fast to exploit new inventions, ideas
- 80 program managers, 6 office managers – flat - only one layer of management between Dir. and operators - $10-50m portfolio per project manager
- $2.5B budget [now $3b]

Cook-Deegan,DARPA Culture, Con't

- Project Managers: sci/tech fanatics
- Base skill – recognizing the greatest talent in the world
- "80 decisionmakers liked by a travel agent"
- "Interactive ('intrusive') style"
- "Within one of the world's most notorious bureaucracies, a tribe of rambunctious technological entrepreneurs"
- Gave us: "e-mail, computer graphics, interactive computing, alternative chip architectures, networking"

Cook-Deegan, DARPA Mission vs. NIH Basic Con't:

- Materials science, space, lazers, microelectronics – all fields led by mission-oriented agencies not basic research approach
- Peer review not the only way
  - ONR: mix of peer review and mission-focus – gave us: "single atom chemistry, 'squeezed' light, acoustics all-fields"
- DARPA: far lower transaction costs than NIH – much lower review costs per science direction

Cook-Deegan, DARPA Mission vs. NIH Basic, Con't:

DARPA – not just alternative to budget pressure and admin. efficiency:

- Preparing grant proposals – major time commitment – 4 or 5 wasted efforts for each funded
- Leo Szilard – Loomis' RAD Lab leader – "Szilard Point"- if only 15 to 20% success rate, waste exceeds benefits
- Reviewers can't tell "truly outstanding from merely excellent"
- Mission/Grand Challenge DARPA approach gets past his dilemma

Cook-Deegan, DARPA Mission vs NIH Basic, Con't:

Case Study – Genome:

- Energy Dept. begins genome project – understands supercomputers
- 1981 – NIH turns down Leroy Hood's/Caltech's plan to automate genome sequencing – in '84 NSF funds it
- 1989 – NIH turns down large scale automated genome sequencing of Hood and Venter – prefers army of grad students – NIH wrong again
- NIH peer review: not fault-tolerant and risk-taking – not always a good model – compare to DARPA successes in tech breakthroughs
- So: not just Admin. Efficiency and Budget– DARPA model at times better

Cook-Deegan – A DARPA at NIH?

- NSF has improved peer review –
  - Rotates grant managers in and out of academia – more flexibility/change
- But DARPA funds mix of small and large grants – more options
- NSF/NIH – grants almost all small
  - Breakthroughs can bubble up through 1000's of small grants – but hard way to get to true widespread innovation
- Real inefficiencies to group processing, as well as advantages of depth
  - DARPA – give power to rising stars/visionaries
  - NIH could use a "DARPA Corps"– run test

Infectious Diseases Society of America

"*BAD BUGS, NO DRUGS* --

As Antibiotic Discovery Stagnates, A Public Health Crisis Brews" (July 2004)

Bad Bugs, No Drugs, Con't:

RESISTANCE ON THE RISE:

- FDA/NIH: drug resistant bacteria are a serious public health threat – few novel drugs in the pipeline to combat them
- 2 million people in US in hospitals will get bacterial infections in hospitals
- 90,000 of them will die
- IOM, FDA: only two classes of antibiotics have been developed in last 30 years; one off those already faced resistance

Bad Bugs, No Drugs, Con't:

- Penicillin resistance story:
- Staph infections spread to the heart, bones, lungs, bloodstream
- 1942 – staph strains resistant to penicillin identified
- By late '60's – 80% of staph bacteria are penicillin-resistant
- Pneumonia: 40% of infections resistant to one drug, 15% to three
- 30 years is typical timeframe for resistant strains to rise to 60%

Bad Bugs, No Drugs, Con't:

THE PIPELINE OF NEW ANTIBIOTICS IS DRYING UP:

- Drug co's withdrawing from antibiotics R&D
- Only 5 antibiotics are in the drug pipeline out of 506 agents in development (2004)
- Antibiotic agents approved dropping fast – '83-87: 16; '98-02: 7
- Antibiotic R&D is lengthy, risky
- Bringing new drug to market: $800m-$1.7b
- Because antibiotics work so well so fast, they produce weak return on investment
- Successful antibiotics too successful to justify investment costs

Bad Bugs, No Drugs, Con't:

GOV'T RESPONSE INADEQUATE

- FDA – has identified problem of innovation stagnation – "applied sciences have not kept up with the tremendous advances in basic sciences"- need new research tools
- NIH Director Zerhouni's "Roadmap" – translational research needed to speed new medicines from bench to bedside – (subject to Institutes' politics – still small funding)
- IFDA – apply S.1375/S.666/Bioshield 2 to infectious diseases

THE BREAKDOWN IN TESTING FOLLOW-ON THERAPIES

FDA, "Innovation/Stagnation - Challenge and Opportunity on the Critical Path to New Medical Products" (March 2004)

FDA, Innovation/Stagnation

- The New Innovation History: slowdown not acceleration in innovative medical therapies reaching patients
- Pattern of breakthrough basic science discoveries, not yielding more effective, safer more affordable medical products
- Medical product dev. path is more complex, inefficient, costly
- New drugs and biologics submitted to FDA in decline
- Costs of product development rising
- Nos. of innovative medical device applications dropping, too
- Because of high dev. costs, innovators concentrating on blockbuster high return products

FDA, Innovation/Stagnation

- Developing products for high public health needs - very difficult
  - Less common diseases
  - Third world diseases
  - Prevention indications
  - Individualized therapies
  - Biothreats

FDA, Innovation/Stagnation

- FDA: applied science for medical product development has not kept pace with basic science advance
  - Point: If our R&D investment is in basic science and not the follow-on process, there will be follow-on problems in the system
  - The new science is not related to tech development
  - Little applied science work on: creating new tools for better answers on safety and effectiveness with faster timeframes, more certainty, lower dev. cost
  - [Note: FDA's "Big Data" personalized medicine initiative – FDA has data, doesn't have R&D funding for computing/analytics]

FDA, Innovation/Stagnation

- Need: new development toolkit
  - New scientific methodologies -- applied areas
  - New animal or computer-based predictive models
  - New biomarkers for safety
  - New clinical evaluation techniques

  for path between science to development to markets
- Medical product dev. process cannot keep pace with basic scientific innovation
  - {legacy of disconnected system}
- FDA - key role in standard-setting - guides dev. programs - needs to be set by better more modern science
- FDA needs new generation of performance standards and predictive tools {who will develop?}

Current FDA initiatives:

- Regulatory Research (previously, "Critical Path") initiative –
  - Underfunded
- "Big Data" analytics of FDA Clinical Trial data for personalized medicine
  - Underfunded

Craig Venter, Con't

- Venter grows up in Milbrae, Calif., both parents ex-Marine Sgt's, workig class, competitive swimmer, almost flunked high school; rebellious
- After high school surfs off Newport Beach near "The Wedge," boardwalk, volleyball, drinking, long hair, hotrod, lives in shack
- Threat of the draft, Vietnam War starts bigtime, goes into the Navy, bootcamp - still has a picture of his drill sgt. in his office
- Scores at the very top of the tests and picks medic training- finds out later this is the most dangerous job there is
- Goes to hospital in DaNang - runs intensive care ward - is there during Tet offensive in '68 - almost overrun- those who decide to live, live
- "Medicine failed us" - crude tools

Craig Venter, con't

- "Amputees and double amputees… because of all of the landmines. It was a failure of our political system. It was a failure of our knowledge of medicine and it was a failure even in some of these cases of psychological support for some of these guys. The whole thing was wrong and I became determined to change my life. I couldn't go back to just being a surfer - that I really loved what I was doing. I loved being able to change people's lives where I could…you try and take solace out of the ones you can help."
- Worked at a village orphanage once a week.
- 12 hours on, 12 off for a year.
- Decides to become a doctor.
- Goes to junior college then college, UCSD.
- Then does science papers with mentor prof's.

Craig Venter, Con't

- PhD at UCSD with mentor prof., then to SUNY Buffalo doing research and teaching
- NIH in 1984, works with Marty Rodbell - molecular bio
- "Vietnam is something I carry with me everyday…the worst thing you had to lose was your life. So I basically viewed every day since I got back as a gift, and I was determined not to waste it or have it ruined by other people's small thinking. I figured what's the worst thing that can happen if I take a risk and fail?Whereas the rest of our structure is built on keeping people in place, because they're afraid to take risks. Every place I've succeeded it was from taking what weren't extraordinary risks."
- Hears about Lee Hood's automated sequencing
- NIH rejects Venter's request for a sequencing machine, buys with with confidential DOD money

Craig Venter, Con't

- Watson of NIH sees Venter's two gene neurotransmitter sequencing data developed over 10 years, and announces before Congress the next day that NIH leads the world and Venter's lab would sequence the human genome.
- Venter is forced because of his Institute affiliation to focus on neurology - NIH can't work across stovepipes
- Develops first bioinfomatics because of need for computing power and new algorithms, then is able to quickly do 100's of new genes via "express sequencing tags" (EST)-thinks of on plane ride
- EST advance disrupts Watson's planning and budget - he attacks Venter for patenting the genome (note NIH patented first and the patent owned by the US) - NIH issue: the discovery is more important than the product; EST not accepted approach
- And NIH's Neurology Institute upset about broad application of Venter's work beyond neurology - outside stovepipe
- Venter leaves NIH with 12 on his team to set up own non-profit research institute funded by venture capital, tied to a separate for profit to develop results
- They link specific gene defects to colon cancer, publish results in *Nature* and *Science* and the race is on

Craig Venter, Con't

- But high stress from VC-named CEO who wants to take credit for EST processing
- Venter meets researcher Hamilton Smith at a conf. and they develop "genome shotgun" method on sequencings not large clones but in pieces
- Article in *Science* makes this EST/shotgun technique clear to all - NIH concerned that an independent lab is undertaking the breakthroughs
- Dept. of Energy not NIH began genome funding because understood supercomputing power - first 3 genomes published with DOE funds
- Working with Perkin Elmer, Venter authorizes the then 3rd largest supercomputer (1.5 teraflops in 1999) to do "genome shotgun" - made by Compaq

Craig Venter, Con't

- Venter negotiates a simultaneous announcement with NIH in 2002 of the genome in *Nature/Science*-what's the meaning?
- Francis Collins - we know something known before only to God
- Venter - "in reconciling things with those men in Vietnam, we try to understand life. We try to explain what it meant….answered by rigorous scientific efforts.
- Celera Genomics grew to $14b market value then crashed in the dotcom crash; Venter was fired; now has foundation.
- The genome Venter published in 2002 is his own genome, with a mix of four other researchers.
- Venter: the power of the unreasonable and the insistent and the risk-taker
- Ideas are a dime a dozen; we'd have ten times the level of innovation if people were less afraid to pursue them - Venter
- "it takes brilliance to know how to execute, and it takes courage of conviction to be willing to do it." - Venter

Why discuss Venter? What does he Exemplify?

- Illustrates innovation structure problems at NIH
- Unable to accommodate radical genome model
  - Requires multidisciplines – computer science allied with biology
  - Hard to accommodate this
- Then illustrates value of a putting a Team B on the problem
  - The two genome projects were duplicative
  - But highly creative science and technology
  - The value of competition around a “Challenge Model”

Bonvillian & Weiss, *Technological Innovation in Legacy Sectors* (chapt. 7)

- ***IT'S NOT JUST NIH – THE HEALTH CARE DELIVERY SYSTEM HAS LEGACY SECTOR FEATURES…***
- **Legacy sector characteristics of Health Care Delivery:**
  - Perverse prices and price structure – prices based not on performance but on amount of services – rewards ever more procedures - inherently inflationary
  - Established infrastructure and institutional architecture – mix of actors that resist change

Bonvillian & Weiss – Legacy Sector Characteristics of Health Delivery, con't

- Powerful vested interests – inflexible professions, insurance firms, etc. that defend existing paradigm
- Sustained by public habits – Medicare is full cost payment system, no patient stake, so ever-more services pile on regardless of outcomes
- Established knowledge base locked in via professions
- Averse to change and innovation – little R&D on care delivery, only on medicines; little focus on preventive health vs. blockbuster drugs

Bonvillian & Weiss - Health as Legacy Sector: Market Imperfections in Health Care Delivery --

- Problem with collective action – decentralized, scattered among thousands of institutions, hard to change
- Governmental and institutional obstacles – health care coverage sends problematic economic signals, public won't tolerate change politically – no competition for performace
- Non-appropriability – electronic records create data for patients that can't be translated into big data for improved patient outcomes – privacy, data access, analytics limits
- Network economies – large scale networks of institutions and actors limit adoption of change – for example in setting standards of performance

PCAST, Propelling Innovation in Drug Discovery, Development and Evaluation (White House 9/26/12)

- Innovation system under stress:
  - NIH budget doubled between 1998-2003, but has not kept up with inflation since then
  - Rising costs of clinical trials – now $1.8B
  - Patent Cliff for Pharmas:
    - Drugs with annual sales of $200B will go off patent in 2010-14
    - Replacement revenues are not available
    - Pharmas are curtailing R&D
  - Venture capital: general decline for all sectors including bio/pharma
    - First time VC deals for biotechs down 29% from 2007-09, and down 40% in health care companies – VCs expect further declines
  - Despite R&D growth in past decades, drug output flat, productivity declining
    - "Eroom's Law" – cost of drug development doubles every 9 years (inverse of Moore's Law)

PCAST Report, con't

- Failure rate for new drugs in clinical trials is increasing –
  - 1993: 82% fail
  - 2003: 91% fail
  - success rate in Stage 3 Clinical Trials declined from 80% in 1993 to 45% now
- Cost of clinical trials is major
  - Top 20 pharmas spend 37% of R&D on clinical trials - $31B/year
- Time to market for drugs growing
  - 8 years to market 50 years ago; over 14 years now
  - Affects patent "exclusivity period" – more time reduces return, raises risk, raises introductory product prices
  - Particularly affects small companies/biotechs that can't manage this risk period

PCAST Report, Con't

- Gap between Research and product development
  - Advances in basic biomedical knowledge not matched by increases in the science technology and tools need for drug development and approval
    - Requires multidisciplinary teams rather than individual investigator model
    - Co's can't invest in this model because the gains of this research, which benefit the overall process, don't accrue to particular firms = it's a "public good"
  - Ideas:
    - NCATS, DARPA and FDA exploring "predictive toxicity" with lab on a chip; enduring clinical trial networks
    - Current patent exclusivity may not be sufficient to create economic incentives for next generation of advances – ex, growing Alzheimer's problem – expand exclusivity period (Orphan Drug Act – 7 years exclusivity from competitor drugs); vouchers for expedited FDA review\
    - New scientific tools for FDA and new surveillance tools once in market

MIT - "The Third Revolution - The Convergence of the Life, Physical and Engineering Sciences" (2011)

- The funding problem faced by NIH
  - Doubling completed by 2003 - stagnation since (aside from $10B Stimulus passed in 2009)
  - No real picture of next advance wave
  - Doubling led by genomics revolution
  - NIH needs a new picture

The 3 Revolutions:

- **first revolution -- molecular biology**
  - probing the inner functioning at the molecular level of diseased cells. **Merger of Physics & Biology: Max Delbruck & Salvador Luria** helped found this movement coming from physics; NIH Cancer Centers a result
- **second revolution -- genome sequencing**
  - remarkable advances on top of learning at the molecular level
  - David Gallus at DOE understood supercomputing and what could be done - begun at DOE – lasts 5 years
  - NIH's Genome Project begun under Watson
  - LeeHood, Craig Venter developed computerized synthesizing
  - Genentech is first biotech built around gen eng
  - New sequencing efforts are now being led by the Broad Institute at MIT - Eric Lander - high throughput, genomes in days not years – lowering to $1000– want sequence in minutes from minimal cost
  - But still built around biological model with computer science as a tool – interdisciplinary not multidisciplinary integration

Some Leaders of Rev's 1 &2: (clockwise) Max Delbruck, Salvadore Luria, Leroy Hood, Craig Venter, Eric Lander

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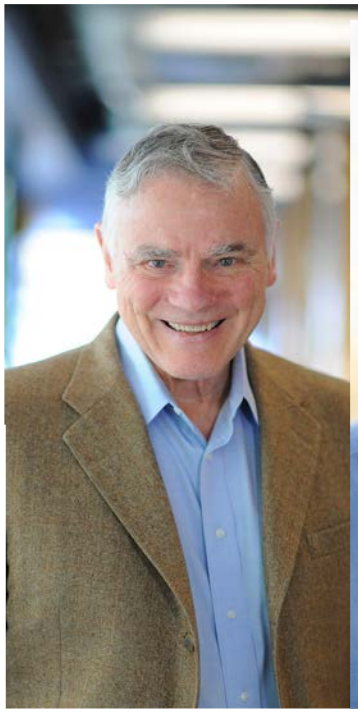

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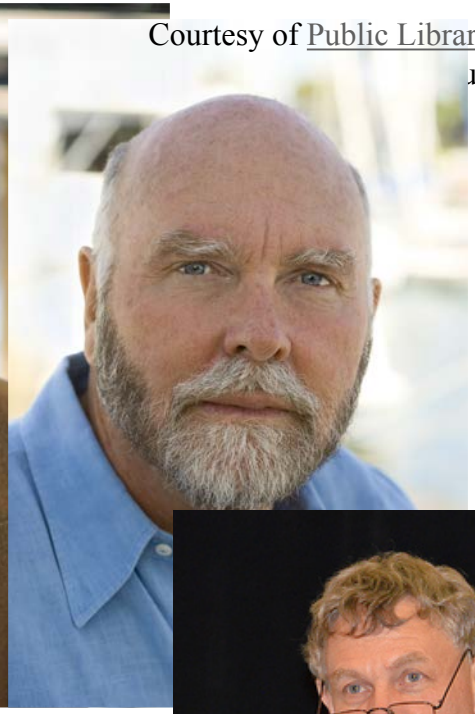

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3rd Revolution:

Combination of Rev 1 & 2 methods and knowledge bases with a systems biology approach with new engineering design model and toolset and physical sciences

- **Brings in engineers not only for devices and but for design of technology – also physical science**
  - **Biological model of complex, dynamic, interactive systems, merged with engineering priortizing and targeting design**
- **The merger of biologists, engineers, physical scientists**
  - **ex: One-third of MIT engineers are now in some level of biology research; BioX Stanford, UChicago, Weist Harvard, GaTech, UMich – but not NIH (NCI, NBIB)**
- **Engineering tools – examples:**
  - **Targeted nanoparticles for delivery across cell walls, membranes**
  - **Polymer nanoparticles and quantum dots for treatment delivery**
  - **Next-generation magnetic nanoparticles for multimodal, non-invasive tumor imaging**
  - **Implantable, biodegradable microelectromechanical systems (MEMS), also known as lab-on-a-chip devices, for in vivo molecular sensing of tumor-associated biomolecules**
  - **Low-toxicity nanocrystal quantum dots for biomedical sensing**
  - **Computational modeling of complex systems**

MIT 3rd Rev. Leaders l-r: Phillip Sharp –Nobel for RNA; Robert Langer, Pres. Medal of Sci., Millenium Prize for tissue engineering; Tyler Jacks, Dir., Koch Institute at MIT; Robert Urban, Koch Inst. now at J&J; Sangeeta Bhatia, MIT Regenerative Medicine; Paula Hammond, MIT, self-assembly molecular design; Susan Hockfield, neuroscience

3rd Rev, con't

- History of other biomedical revolutions
  - Molecular biology
  - Genomics
  - Essentially built new knowledge bases
- Convergence - different - could be new therapies plus knowledge base
  - New technologies shifting over from engineering
  - Imaging, sensors, nano, simulation, modeling, probability
  - Complex system bio model joins engineering design model
- Way of looking at new strands: synthetic bio, nano-bio, systems bio, bioinfomatics, computational bio, tissue engineering

3rd Rev, con't

- **Will Convergence play a role in the medical cost problem?**
  - **Cost problem due to lack of any incentives for cost control - system only interested in adding services**
  - **But: health care reform: financial plumbing only - no innovation**
  - **Innovation can drive down cost and improve health – examples:**
    - **Heart disease: $4/person/year - fatal heart attacks and strokes down by 63%**
    - **Life expectancy: up 6 years over last 30 years**
    - **HIV/Aids - manageable outpatient disease in U.S.**

3rd Rev, con't

- **Health reform and innovation:**
  - **Healthier aging**
  - **Key spread the demographic bulge over longer period - keep aging in workforce**
  - **If baby boom gen can be made healthier, makes demographic shift more manageable**
- **Convergence in other fields:**
  - **Environment, Climate, Food Supply, energy, biofuels**
    - **Ex: self assembled virus batteries**
  - **Physical science affected by complex biological systems model**

Policy steps for convergence:

- **Centers across stove-piped IC's and agencies – think tank with cross-agency personnel**
- **Reform peer review;**
- **Multi-PI grants**
- **Pooled funding across IC's**
- **Need larger-scale multi-disciplinary science (along with RO1's)**
- **Education in convergence – multi-disciplinary "convergence creole"**

Developments re: Convergence

- White House developed "Brain" and "Precision Medicine" initiatives based on Convergence Model
  - include NIH, DARPA, NSF
  - Re: Brain – significant NIH planning efforts – 2 institutes adopting model – but limited new funding
- DARPA – new "Biological Technologies" office opened in 2014
- NCATS founded at NIH to pursue "translational" research
- Broad Institute pursuing big data and genomics research toward personalized medicine
- Some 15 univ's now have research efforts organized on convergence model
- National Academy and AAAS reports on convergence

Wrap-Up: Class 9

The Outlook:

- **Demographics Revolution Ahead**
- **Medical system is not affordable for the country**
- **New biothreat problem**
- **Innovation system is one way out**
- **But Innovation system slowing**
- **There is a gap between genomics advances and translating them into actual medicines**

Wrap-Up, Con't:

SO: 2 Trainwrecks ahead:

(1) Innovation trainwreck:

- **Economic model for biotechs/pharmas requires blockbuster-sized markets**
- **As discussed, this model leaves out:**
  - **Most infectious diseases**
  - **Small population diseases**
  - **Remedies that serve smaller than target population market taken off market as dangerous**
  - **90% of world medical R&D spent on 10% of diseases**
- **No sign yet of individualized/genome based medicine and no economic model yet for it**
- **Litigation threat makes firms risk adverse**

(2) Cost/Demographics trainwreck

Wrap-Up, Con't:

NIH Needs –

- Cross-cutting R&D across stovepipes
- Cross-agencies R&D
- Cross-Disciplinary R&D
- Stronger NIH Director for Translational Research
- Public-Private Partnerships for gap between basic and applied
- DARPA capability for
  - High-risk, high-payoff research
  - Connected Challenge model
  - Project manager not peer review
  - Leverage stovepipe collaboration

Wrap-Up, Con't:

Expand the Innovation Search of Biotechs Beyond Current Market Definitions -

Create market pull not just R&D market push

- **New menu of incentives - guaranteed contract for workable product, PLUS:**
  - **Keep competitive model not Defense Contractor model**
  - **Gov't Procurement for non-markets**
  - **IPO rights/Patent Wild Card**
  - **Tax incentives**
  - **Extend incentives to Research Tools not just medicines**

Despite the Problems, New Promises…

- **NIH ex-Director Dr. Elias Zerhouni:**

  "As science grows more complex, it is also converging on a set of unifying principles that link apparently disparate diseases through common biological pathways and therapeutic approaches. Today, NIH research needs to reflect this new reality."

COURSE WRAP-UP --

Summary of key ideas:

Class One

- **Class 1: Economic Growth Theory and the role of Innovation in growth**
  - **Classical Economics: capital supply and labor supply - equilibrium system**
  - **Solow: Technological and Related innovation = 1/2, 2/3's growth**
  - **Romer: Human Capital Engaged in Research**
  - **So: R&D and the talent behind it - the 2 direct innovation factors**

Class Two:

- **Class 2:**
- **Indirect Elements; Innovation as an Ecosystem**
  - **indirect elements, gov't and private sector**
  - **Nelson: national innovation system**
  - **how do you cross the Valley of Death in a disconnected model?**

Classes Three through Five:

- **Classes 3 & 4: Case Studies -**
  - **manufacturing and services – the crucial role of innovation policy**
- **Class 5: Innovation Organization**
  - **Associationalist model; public private partnership**
    - **Vs. Conservative model**
    - **Vs. Nat'l Security model**
  - **Innovation - look at at the institutional and personal levels**
  - **Institutional level - after WW2, V. Bush splits R from D**
  - **Stokes – US: Disconnected model - creates tech transition problem**

Class Six:

Class 6:

- **How to cross the "Valley of Death" (Branscomb/Auerswald)?**
- **Associationalist programs of 80's, 90's**
- **"Is war necessary for economic growth?" – Ruttan**
- **In-Q-Tel – the most radical, interventionist model – gov't VC "picking winners and losers"**

Class Seven:

- Class 7 - Organization of Innovation at the Face to Face Level -
  - Innovation is people - not institutions
  - Great Group theory
  - Great group rule-sets: flat collaborative non-hierarchial, mix of disciplines, room for leadership
  - The Third Direct Innovation Factor: Innovation Organization

Class Eight:

- **Class 8 - DARPA as renewal of the WW2 connected model**
  - **Combines institutional connectedness and sponsors great groups**
  - **Operates at both levels of innovation – institutional and personal**
  - **Role of Technology Visioning (Carleton)**

Class Nine:

- Class 9: Applying the Innovation Framework – NIH
  - A disconnected model – 27 Institutes and Centers – not cross-cutting
    - Basic research model, non interdisciplinary
  - Pending 3rd Revolution – convergence – can it adopt?
  - Institutional stovepipes vs. connectedness
  - Can NIH sponsor great groups – then: ability to scale?

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