The slowing of treatment discovery, 1965–1995

The discovery of effective disease treatments has slowed. This may be related to a misunderstanding of the treatment-discovery process, and an underappreciation of clinical investigations and off-label drug studies.

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In the United States, two goals motivate our national effort in biomedical research: The acquisition of knowledge about how the body works, and the discovery of ways to prevent or treat disease. There can be no doubt that this effort — which each year now expends around eleven billion dollars of public funds through the National Institutes of Health alone — succeeds magnificently in attaining the first goal. Our analysis indicates, however, that successes in the second have been surprisingly infrequent during the past three decades, in marked contrast to the three that preceded them, and in spite of a more than fourfold real-dollar increase in federal research support. Few effective treatments have been discovered for the diseases that contributed most to morbidity and mortality in 1965, or for newly recognized killers like Alzheimer's disease and AIDS. Although life expectancy has, in fact, increased since 1965, this increase resulted not from the discovery of effective treatment for previously untreatable diseases but from the widespread application of established preventive measures, such as the management of hypertension and the continuing development of vaccines (for example, for pneumococcus and hepatitis B); improvements in the diet and the distribution of medical care; the invention of novel diagnostic techniques, like those based on imaging; and major advances in surgery and anaesthesia, particularly affecting cardiology, orthopaedics, and organ transplantation. None of these changes resulted principally from discoveries made in biomedical research laboratories. It may turn out that current, cutting-edge bench findings relating, for example, to gene therapy, or apoptosis, will indeed revolutionize treatment discovery in the future. However, prophecy is notoriously unsuccessful in this arena, and attempts at analysing why so few diseases have become treatable at a time of great growth in fundamental biomedical knowledge must focus on what actually has happened, not on what we hope will happen.

What went wrong? In retrospect it appears that a faulty formulation — about how public investment in science should best be applied to conquer disease — gained hegemony. And since the federal contribution constituted so large a proportion of the total funds available for biomedical research, implementation of this paradigm ultimately caused major distortions in the treatment-discovery infrastructure. That view of how progress is made in medicine was born in 1945, when President Harry Truman's science advisor, Vannevar Bush, wrote a report titled *Science, The Endless Frontier*. It held that the most effective strategy was not to require scientists to relate their research to specific societal missions — like finding treatments for pellagra or hypertension or AIDS or Alzheimer's disease — but instead to encourage them to work independently, follow their curiosity in choosing what to examine, and to strive only for scientific excellence. Moreover the government, in distributing public funds, should implement this strategy, and should not mount "Manhattan Projects" (or "Wars on Cancer") for individual diseases, similar to the one that Dr Bush had so successfully directed for building atom bombs. In the present article, we document the decline in treatment discovery, identify the principal components of the discovery process and consider how application of the "Bush paradigm" may have contributed to the lack of success of the past thirty years. Treatment discovery turns out to be very much a directed or mission-oriented enterprise, requiring the participation of investigators committed to that task.

Table 1 Diseases that became treatable, 1935–1965

Disease	Treatment
Hypertension	Diuretics, beta-blockers
Hyperthyroidism	Radioactive iodine, propylthiouracil
Childhood leukaemia, Hodgkin's disease	Chemotherapeutic agents + combinations
Depression	MAO inhibitors, tricyclics
Psychosis	Dopamine receptor antagonists (Chlorpromazine; haloperidol)
Epilepsy	Phenobarbital, diphenylhydantoin
Parkinson's disease	L-DOPA
Bacterial infections	Antibiotics
Fungal infections	Amphotericin
Tuberculosis	Streptomycin, INH, PAS
Phenylketonuria	Low-phenylalanine diet
Dermatologic disorders, hepatitis	Steroids (for example, prednisone)

Treatment discovery pre- and post-1965

The period between 1935 and 1965 constituted a Golden Age for treatment discovery (Table 1), and although a number of diseases — including behavioural disorders like alcoholism and drug abuse, and many cancers — remained a scourge (Table 2), nevertheless there seemed to be every reason for optimism that, if the Congress would continue to expand their financial support, these diseases would also be conquered by the biomedical research institutions already in existence.

This has not happened. Even though many useful new drugs and important off-label uses for old drugs have been discovered since 1965, very few of these constituted first-ever or even very novel treatments for poorly treated diseases. American research during this period did generate the first effective drug for herpes simplex (acyclovir); a novel chemotherapeutic agent (cisplatin); compounds which may be useful in treating AIDS (AZT) and benign prostatic hypertrophy (finasteride); and, through biotechnology, growth factors like erythropoietin which previously were too expensive for routine use. However, an examination of a list of the most widely used agents (Table 3) that became available since 1965 indicates that these agents either provided only incremental advances over existing effective therapies (for example, the ACE inhibitors and calcium channel blockers for hypertension or angina,

previously treatable with diuretics or beta-blockers; gemfibrozil and lovastatin to lower blood lipid levels, previously managed using nicotinic acid or cholestyramine; fluoxetine for depression, also well treated in most patients with MAO inhibitors or tricyclic compounds; and ranitidine, omeprazole, or famotidine supplementing cimetidine for peptic ulcer), or were the products of European investigators (cimetidine) and companies (clozapine, propranolol, cyclosporine, omeprazole, sumatriptan), unsupported by publicly funded research programs analogous to those of the NIH.

As discussed below, important treatment advances have also been made since 1965 by clinical investigators who discovered new, off-label uses for existing drugs (for example, the Australian finding that peptic ulcer could be treated with antibiotics). However, this approach to treatment discovery has received minimal federal research funding, and been underwritten largely by a tenuous source, the test subjects' own third-party payers. The rise of the biotechnology industry has offered great promise for treatment discovery in that its techniques allow macromolecules — a largely untapped source of potential drugs — to be produced relatively inexpensively. However, to date almost all of the commercial products of this industry have constituted either 'old' drugs synthesized using a new chemistry (for example, insulin, growth hormone and factor VIII) or endogenous growth factors, and immune-active compounds initially produced without documented clinical applications, and then made available to clinical investigators who discovered indications for them by off-label research (for example, the interferons, interleukin-2)[1].

Is the problem simply that all of the easy disease problems have been solved? This seems unlikely. Some recent treatment discoveries have also been "easy" in the sense of requiring no new basic science, for example, anti-inflammatory drugs (like ibuprofen) to treat cystic fibrosis, or antibiotics (like tetracycline) to treat peptic ulcer. Moreover, a number of complex and poorly understood neoplastic (Hodgkin's disease), degenerative (Parkinson's) and genetic (phenylketonuria) diseases became treatable decades ago. The easy versus hard distinction assumes that a disease must first be understood on a molecular level before a treatment for it can be invented. History tends to teach otherwise, as discussed below. Most of the most successful new drugs of the present era have been based on research strategies that date back to the 1940s — for example, enzyme inhibition, receptor blockade or smooth muscle relaxation. The pharmaceutical industry continues to use these strategies, and the end of the Golden Age in drug discovery clearly did not coincide with a major transfer of resources to entirely new approaches that might have required decades to pay off.

Table 2 Diseases that remain poorly treated

Lung, breast, ovarian, brain, prostate cancers
Congestive heart failure
Alzheimer's disease
Stroke
Alcoholism
Drug abuse
Amyotrophic lateral sclerosis
AIDS
Emphysema
Lupus erythematosus (related immune-complex diseases)

Discovery of new medical treatments

Novel treatments can be based on new chemical entities, or known drugs for which new uses have been found. Our analysis indicates that new drugs usually arise from a dynamic interaction, described below, among basic and clinical scientists, often working in academic institutions, and applied pharmaceutical scientists working in industry. The initial observation that starts the drug discovery process can be either clinical or basic; however, an essential dialogue between the disciplines ultimately ensues. Treatment discovery by off-label testing tends, in contrast, to be the sole province of clinical investigators, who note that a drug given to treat one disease happens to confer unanticipated benefits in another or speculate that a poorly treated disease involves a treatable pathophysiologic mechanism (bacterial infection in peptic ulcer or autoimmunity in multiple sclerosis). Alternatively it can originate in new basic-science insights about an existing drug's mechanism of action, which suggest that the drug might also be useful in a class of diseases other than the one for which it was developed (aspirin to inhibit platelet aggregation after myocardial infarction; methylprednisolone to treat spinal cord injury), or just in clinical serendipity (the testing on arthritic patients of an antibiotic — minocycline — that also happened to be a peptidase inhibitor). Off-label treatments may also — particularly in cancer chemotherapy — involve combinations of drugs manufactured by two or more companies; they remain 'off-label' because neither company elects to underwrite the large-scale phase III studies required to win FDA approval of their new use.

In drug discovery, 'basic science' encompasses two major levels of exploration: molecular analysis, which identifies and characterizes macromolecules and the ligands that interact with them, and the integrative sciences like physiology and pharmacology, which identify and characterize biologic systems. Both molecules (for example, those in viruses) and systems (those that control blood pressure, or blood cholesterol levels) can constitute sites of drug action. Clinical scientists demonstrate that a particular molecule or system is abnormal in patients with a particular disease, or at least is critically involved in the disease process, and propose that it might thus constitute a useful target for therapeutic interventions. Applied pharmaceutical scientists then establish screening systems for identifying compounds that can act on the molecules or systems, generate new chemicals (from natural or synthetic sources) to be tested, and do toxicologic testing of those displaying useful activity in the screens. Clinical investigators then determine a candidate drug's safety, efficacy and benefit/risk ratio. Sometimes a biologic insight — such as the tendency of a therapeutic class of drugs to cause a characteristic disturbance in the behaviour of animals or cells — can become the basis of a screening system which, many years later, facilitates discovery of a candidate drug in the absence of knowledge about that drug's biochemical mechanism of action. Many important new drugs (clozapine, cyclosporine, Taxol) continue to be discovered in this manner. Drugs also arise from 'folk medicine' observations of clinical responses to natural products (digitalis, atropine, reserpine) unsupported by any *in vitro* or whole-animal data.

The dialogue between basic, clinical and applied researchers leading to drug discovery is a disordered one that invariably occurs over extended distances and times. However, this need not be the case. Arguably, the drug discovery process could be accelerated by planning

and coordination among the various professional groups involved. Novel drug applications, be they new drugs or new off-label uses, absolutely require the participation of clinical investigators, a professional group that, for reasons described below, has come to be in such short supply as, conceivably, to be limiting. Drug discovery could also be accelerated, according to the pharmaceutical industry, if some of the funds now expended in order to satisfy questionable regulatory requirements could be saved and committed to research. However one cannot predict how those savings would be used, since pharmaceutical companies are, after all, companies, and are required to seek profits: If developing an additional second- or third-generation drug, in-licensing a drug invented by a foreign company, or producing a once-a-day preparation to replace one taken twice daily, is more likely to be profitable than establishing a long-term research program to find the first effective treatment for an untreatable disease, economics may continue to dictate the former choices unless society elects to provide financial incentives for the latter.

Bush and biomedical research

In *Science, The Endless Frontier*, Bush articulated a view of progress — towards solving society's science-related problems — which holds that science begets technology, and that the surest way to attain technologic solutions was to build the strongest possible science base. This was to be done by training and nurturing a large cadre of fundamental scientists who would independently explore scientific questions of their own genesis and after receiving the critical approval of their national peer community, using government funds. The 'harder' the science they pursued — the more it resembled physics ('physics envy') — the stronger its claim for public support. Bush rightly foresaw that this strategy would be highly effective for accumulating knowledge, and in some fields — such as physics — there may indeed be enough of a continuum between the methods and concepts of basic and applied research to allow an easy flow between the acquisition of knowledge and its application. Bush probably did not perceive, however, that there is a distinct Method of Medicine, encompassing, among other disciplines, epidemiology, clinical physiology, psychology and the natural history of disease; that this method includes but far transcends the Method of Biology; and that theoretical biology alone could no more be expected to generate treatments for human diseases than theoretical architecture alone could design particular bridges. In trying to find treatments for AIDS, it is useful to know that HIV produces reverse transcriptase and a characteristic protease, but it is also useful to have access to clinical evidence that the patient's T-cells are engaged in a 10-year battle with free virus particles, during which a treatment that gave the T cells the edge might change the course of the disease.

Ongoing analysis of NIH funding patterns suggests that the Bush paradigm still rules, often to the detriment of projects involving research on physiologic systems or on human subjects — both of which are critical for the discovery of new treatments. Some of these biases and their consequences have been analysed during the past year by federal panels: An NIH-sponsored committee[2] concluded that grant applications to conduct 'patient-oriented research' fare less well than 'basic-science' applications because of the skewed composition and disciplinary biases of review panels, and proposed that special panels, disbursing funds sequestered for this specific purpose, be established to support this research. And an Institute of Medicine committee noted[3] the paucity of NIH-funded mechanisms for training and then supporting young clinical investigators, compared with the array of programs for their peers in, for example, molecular biology, and related this financial uncertainty to the small number of tenure-track positions that universities — fearing the need to

Table 3 'Blockbuster' drugs, 1993

Rank	Drug	Category	Company	Sales (US$ million)
1	Zantac (ranitidine)	anti-ulcer	Glaxo	3,520
2	Procardia/Adalat (nifedipine)	cardiovascular	Pfizer/Bayer	2,100
3	Vasotec (enalapril)	cardiovascular	Merck	2,065
4	Epogen/Procrit (erythropoietin)	anaemia	Amgen/Johnson & Johnson/others	1,806
5	Capoten (captopril)	cardiovascular	Bristol-Myers Squibb/Sankyo	1,800
6	Pravachol/Lipostat (pravastatin)	lipid lowering	Bristol-Myers Squibb/Sankyo	1,651
7	Losec/Prilosec (omeprazole)	anti-ulcer	Astra/Merck	1,642
8	Humulin/Novolin (human and animal insulin)	antidiabetic	Lilly/N Nordisk/others	1,610
9	Cardizem/Herbesser (diltiazem)	cardiovascular	MMD/Tanabe/others	1,544
10	Intron A/Sumiferon/Roferon-A (alpha-interferon)	anticancer	S-Plough/Roche/Sumitomo/others	1,466
11	Mevacor (lovastatin)	hypolipaemic	Merck	1,310
12	Pepcid/Gaster (famotidine)	anti-ulcer	Merck/Yamanouchi	1,260
13	Tagamet (cimetidine)	anti-ulcer	SmithKline Beecham	1,208
14	Cipro (ciprofloxacin)	antibiotic	Bayer	1,200
15	Novolin (human insulin)	antidiabetic	N Nordisk/Lilly	1,170
16	Zovirax (acyclovir)	antiviral	Wellcome	1,163
17	Prozac (fluoxetine)	antidepressant	Lilly	1,150
18	Voltaren/Emulgel (diclofenac)	NSAI	Ciba	1,140
19	Ventolin/Proventil (salbutamol)	bronchodilator	Glaxo/Shering-Plough	1,137
20	Augmentin (amoxicllin + clavulanic acid)	antibiotic	SmithKline Beecham	1,130
21	Omnipaque (iohexol)	contrast agent	Nycomed/Daiichi/Sterling/Schering	1,125
22	Ceclor (cefaclor)	antibiotic	Lilly/Shionogi	1,067

Source: Scrip's 1995 Yearbook.

support grantless professors — have generated for such investigators. The committee, Integrative Medical Research Initiative, whose manifesto was endorsed by some 600 signatories, has described the disinclination of NIH panels to support basic research on physiologic systems, and has initiated lobbying efforts to overcome the effects of this bias[4].

Examples abound of the consequences of implementing the Bush paradigm. The Alzheimer's Disease Research Centers of the National Institute on Aging, which administers hospital-based programs that bring together clinical and basic scientists to investigate Alzheimer's disease, received 10.5% of that Institute's budget in 1991, but only 8.3% in 1994. The proportion of total extramural NIH research dollars committed to the NIH Division, the National Center for Research Resources, which funds General Clinical Research Centers and the expensive instrumentation sometimes needed for clinical studies, fell from 6.5% in 1989 to 4.0% in 1994, and the number of General Clinical Research Centers fell from 93 in 1970 to 75 in 1995. Also, fewer than 10% of all of the graduates of NIH-funded M.D./Ph.D. programs ever thereafter do studies on human subjects, most choosing instead to base their careers on their Ph.D. credential. Outside experts who review NIH grant applications are instructed to consider the "scientific, technical, or medical significance and originality" of the proposed research; they are not invited to evaluate its likely importance for treatment discovery nor, for the most part, would they be qualified to do so. Most grant applications do proclaim the disease-relevance of the studies they propose; however, this has become a convention that, for the most part, is taken seriously neither by applicants nor reviewers. Indeed, applications which propose identifying possible targets for drug actions — by measuring levels of endogenous compounds in people with a disease — are often dismissed as being 'phenomenologic' and of little scientific interest.

Who pays for studies on off-label uses?

Clinical investigators working independently or, for cancer chemotherapeutic agents, as members of NIH-sponsored consortia, discover new therapeutic uses of known drugs. This process is limited probably by the availability of both qualified investigators and public funding. Occasionally the known drug is still on patent, and the off-label testing is supported by the company that holds the patent, and followed by submission of a formal New Drug Application (NDA) to the Food and Drug Administration (for example, fluoxetine for bulimia, or captopril for diabetic nephropathy). However, more commonly patent protection for the chemical entity no longer exists (even though the discoverer of its new use could patent that use if he or she chose to). Thus, whereas industrial support cannot be obtained, and public support is also usually lacking, insufficient data are collected to support an NDA. The result of this is that the drug's new indication cannot be proclaimed on its label, leaving physicians to learn about this new use from the medical literature or from medically sophisticated lay publications.

In keeping with the Bush formulation of the government's proper place in biomedical research, the NIH's involvement in supporting clinical, off-label drug research has been small. Sometimes this institution, acting alone or in consort with the Veteran's Administration, will sponsor a large-scale study of a proposed off-label drug use. But such sponsorship usually covers only administrative expenses, and not the much more expensive costs of treating the test subjects. Until recently, these have been reimbursed by third-party payers, or underwritten using hospital profits. However, this situation is changing: Medicare no longer covers the subject costs of clinical research (for example, on new uses of Taxol to treat diseases for which it is not currently indicated, such as Kaposi's sarcoma associated with AIDS). If other third-party payers follow Medicare's lead, much off-label drug research will cease altogether unless the public, perhaps through the NIH, starts to cover these costs. Cuts in the Veteran's Administration budget and the worsening financial situation of private hospitals will only exacerbate this problem. It is interesting to note that some medical fields, such as psychiatry, have traditionally lacked any continuing federally mandated mechanism for underwriting large-scale studies of off-label drug uses, perhaps explaining the lack of comparison data to help the psychiatrist, for example to choose among the myriad anti-depressant drugs now available, or the lack of more than anecdotal evidence that serotonin-uptake blockers ameliorate character disorders.

Promoting treatment discovery

Congress' intent that resources allocated for biomedical research should promote treatment discovery — as well as the acquisition of fundamental knowledge — is clearly stated in each of the bills that it passes funding the NIH, and this goal continues to have the broad, if perhaps decreasing (because of converts to alternative medicine) support of the American public. Can the distortions in infrastructure which limit treatment discovery be repaired by modifying the NIH's priorities without jeopardizing the ability of our biomedical research institutions to continue to do what they do so well? No matter how unlikely it seems, surely entirely new funds for infrastructure repair would make this task easier. Perhaps other changes can be made, and the recent appointment of a committee to advise the NIH on clinical investigation suggests that changes are in the offing.

But more needs to be done. If decades of experience affirm the inadequacy of the Bush paradigm, then is it not appropriate for the government to adopt a new formulation of how it can best promote treatment discovery? We believe this is the case, and hope that the next few years will witness a national conversation, buttressed by an historical analyses of the circumstances that have most often been associated with success, and one that will give birth to a new paradigm. Perhaps new institutions will be needed. Perhaps existing ones can be modified. We will know that America has chosen the proper course if the record of treatment discovery in the next decades approaches that of the Golden Age of the mid-twentieth century.

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1. A full listing of biotechnology drugs is available from the authors.
2. Williams, G.H. *An Analysis of the Review of Patient-Oriented Research (PR) Grant Applications by the Division of Research Grants, NIH* (Clinical Research Study Group, NIH, 1994).
3. Kelly, W.M., and Randolph, M.A *Careers in Clinical Research: Obstacles and Opportunities* (National Academy Press, Washington, 1994).
4. Iobe, P.C. *et al.* The essential role of integrative biomedical sciences in protecting and contributing to the health and well-being of our nation. *The Physiologist* 37, 79–84 (1994).

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