
DataWatch

Each quarter, Health Affairs reports on new developments in one of four sectors of the health sphere: health care innovation in Summer, national health care spending in Fall, health personnel in Winter, and health status and health care utilization in Spring. In this issue, J. Leighton Read and Paul M. Campbell update trends in health care technology and manufacturing and discuss the impact of competition. Pamela Farley Short of the National Center for Health Services Research and Health Care Technology Assessment reports on trends in employee benefits. Finally, Lynn Gruber, Maureen Shadle, and Cynthia Polich of InterStudy trace the history of the health maintenance organization (HMO) movement from the 1970s to the present.

Health Care Innovation: A Progress Report

by J. Leighton Read and Paul M. Campbell

Few enterprises present more opportunities for meaningful innovation than those that deal with the prevention, care, or amelioration of human disease. Americans are apparently willing to spend a great deal to achieve such innovation via both public and private institutions. Yet it is difficult to get a precise handle on what is gained from this investment. As described in today's popular management books, innovation proceeds in a messy, unpredictable fashion. Do we get our money's worth?

From a health policy perspective, the balance between forces that accelerate or retard health care innovation should be subject to continuous scrutiny. Policymakers should be concerned that the forces driving research and development (R&D) investment are well coordinated with society's needs. Furthermore, innovation must represent a balance among competing constraints, including opportunities to fund innovative work unrelated to health; the cost, risks, and benefits of applying innovations; and the limits of acceptable research on humans and animals.

Unfortunately, reliable yardsticks to measure innovation are not read-

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ily available. The link between new ideas and better health or lower costs is often difficult to draw. What we can do is examine R&D spending data, recognizing that spending is not a measure of innovation but, rather, of commitment to innovation.

Some “process measures” also are available. Patent approvals signal certain types of activity, but not all forms of innovation are patentable. And many patented ideas never find their way into use. In the heavily regulated pharmaceutical and medical device industries, government filings and approvals can serve as progress reports. Finally, growth in sales dollars offers an impure measure of innovation for products such as drugs and devices. Unfortunately, similar measures are not readily available for innovations in health care services. This important component of health care innovation therefore will not be dealt with here.

As in previous Summer issues of *Health Affairs*, this DataWatch will examine some of these vital signs with emphasis on federal sponsorship of biomedical research, pharmaceuticals, biotechnology, and medical devices. In this issue, the data are organized by concept, rather than industry.

Investment In Research And Development

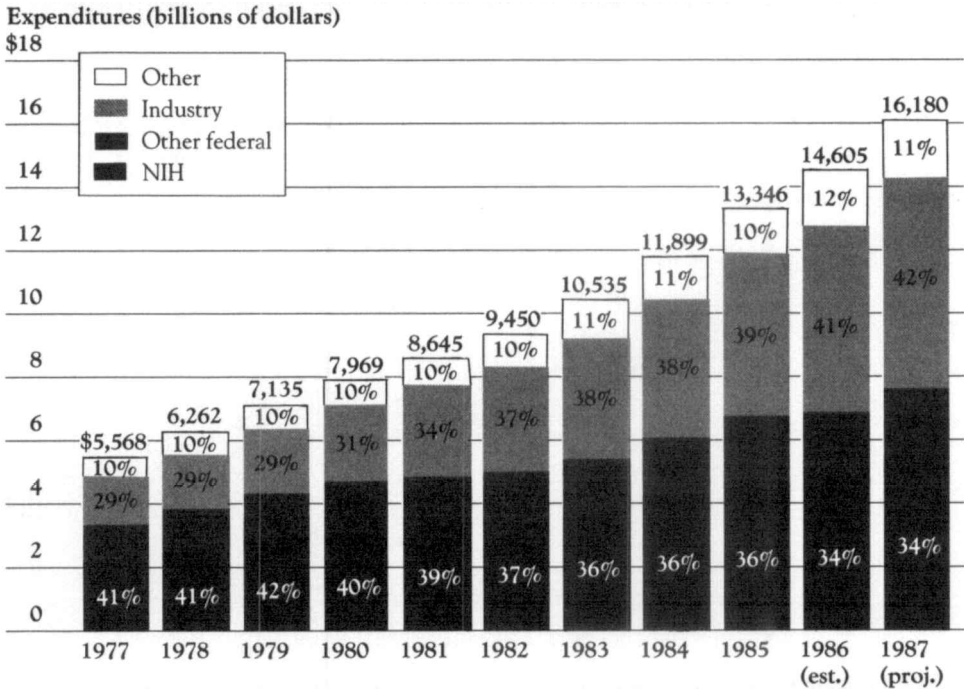
According to the National Science Foundation, U.S. R&D expenditures will exceed \$131 billion in 1988.¹ Roughly 13 percent will be directed to biomedical projects. Each year, the National Institutes of Health (NIH) tally various contributions to this effort. As shown in Exhibit 1, the federal share of this investment fell below 50 percent in 1984 and continues to decline. According to the Pharmaceutical Manufacturers Association (PMA), 1988 marks the first year that the major drug companies will spend more on R&D than will NIH.²

NIH spending in 1987 exceeded \$5.5 billion out of a federal total of \$7.6 billion.³ The estimate for 1988 NIH spending is \$6.3 billion. Government agencies committing more than \$100 million per year to health-related R&D include the other branches of the Public Health Service, the Departments of Defense and Energy, the National Aeronautics and Space Administration (NASA), and the Veterans Administration.

Exhibit 2 shows how the site of performance varies by source of funding. While most work sponsored by NIH is carried out in colleges and universities (61 percent), a staff of over 10,000 employees sustains its intramural programs. Of these employees, 18 percent have doctoral-level degrees.

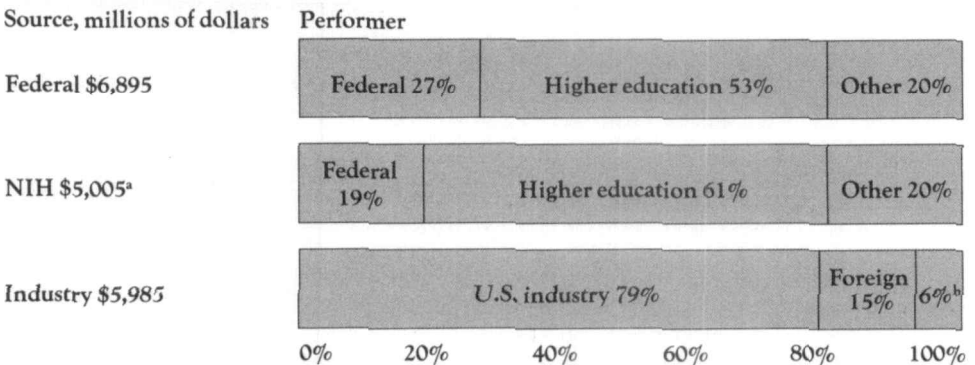
Pharmaceutical companies account for 76 percent of the industry contribution, employing approximately 40,000 in domestic R&D activi-

Exhibit 1
National Support For Health R&D By Source, 1977-1987



Source: National Institutes of Health, NIH Data Book (1987).

Exhibit 2
National Support For Health R&D BY Source And Performer, 1986, Estimated



Source: National Institutes of Health, NIH Data Book (1987).

^a Includes research grants (74%) contracts (7%) intramural research (12%) and appropriate management costs, interagency agreements, and so on (7%).

^b Other.

ties.⁴ The drug industry does most of its own R&D. Almost one dollar in five goes to foreign branches of U.S.-based companies.⁵ Exhibit 3 shows that pharmaceutical R&D expenditures as a percentage of sales have risen steadily over the past decade. In comparison, a survey of sixteen publicly traded medical equipment firms showed that R&D as a percentage of sales averaged 5.5 percent in 1986, down from 7.1 percent in 1984.⁶ Within the device industry, relative R&D expense varies with company size, with smaller companies spending almost double the industry average.⁷ For comparison, the nation spends about 3 percent of its total health care bill on R&D, considering all payers.⁸

Exhibit 3

Sales And R&D Expenditures For Pharmaceuticals, 1981-1987, Millions Of Dollars

	1981	1982	1983	1984	1985	1986	1987 ^a
Worldwide sales	\$23.530	\$25.654	\$27.506	\$29.854	\$32.026	\$37,137	\$41,246
Foreign sales	45.3%	41.6%	37.8%	35.1%	33.9%	34.3%	31.3%
Domestic R&D as percent of domestic sales	13.1%	13.8%	14.4%	14.4%	14.8%	14.8%	15.1%

Source: Pharmaceutical Manufacturers Association, 1986-1987 Members Survey (1987).

^aBudgeted.

A crude audit of the balance between the national burden of illness and R&D expenditures can be constructed from data published by NIH and the PMA. In Exhibit 4, the national burden of illness is represented by a measure of mortality (the percentage of all deaths due to conditions falling into various broad categories) and a measure of morbidity (the relative prevalence of selected chronic conditions). In broad terms, R&D expenditures follow mortality rankings fairly closely. Heart disease is the leading cause of mortality. Diseases lumped together in the category cancer/endocrine/metabolic diseases are second. This rank matches the aggregate drug industry budget. In the area of devices, cardiovascular products are the second most frequently received premarket applications at the Food and Drug Administration (FDA). Cardiovascular companies spend about 9.8 percent of the sales on R&D and about 55.8 percent on new product development. For NIH spending, these two categories appear to be reversed. Otherwise, the relative rankings are similar, with the exception of disproportionate industry spending in the area of infectious disease.

In contrast, arthritis and other musculoskeletal conditions are the most prevalent forms of chronic morbidity, followed by respiratory conditions. One might conclude that these problems should receive increased

Exhibit 4**National Burden Of Illness And R&D Expenditures**

Disease category	Relative percent burden of illness		Relative percent R&D expenditures	
	Mortality	Morbidity b	NIH	PMA
Infectious disease	1%		4% ^c	14%
Central nervous system, senses	9	42%	11 ^d	14 ^e
Cardiovascular	40	18	13 ^f	26
Neoplasms/endocrine/metabolic	22	3	27 ^g	18
Gastrointestinal/genitourinary	7	20	3 ⁱ	
Respiratory	5	1	6 ^h	2
Other	16	16	40	16
Total	100	100	100	100

Source: National Institutes of Health, *NIH Data Book* (1987) and Pharmaceutical Manufacturers Association, *1985-1987 Members Survey* (1987).

^a From 1984 U.S. mortality data, National Center for Health Statistics (NCHS).

^b For this analysis, prevalence data for selected chronic conditions from the 1985 NCHS Health Interview Survey were grouped into categories and expressed as a percentage of all conditions reported. Mental conditions and cancer were not included.

^c National Institute of Allergy and Infectious Diseases obligations excluding immunology, with proration of intramural research and research management and support.

^d National Eye Institute and National Institute of Neurological and Communicative Disorders and Stroke obligations.

^e Includes research on anti-inflammatory drugs.

^f National Heart, Lung and Blood Institute (NHLBI) obligations excluding lung disease.

^g National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) obligations excluding digestive and kidney.

^h NIDDK obligations excluding diabetes, endocrine, and metabolism.

ⁱ NHLBI obligations excluding heart and blood.

attention. Unfortunately, the simple morbidity rankings in Exhibit 4 misrepresent relative policy importance: a minor tendonitis condition is given the same weight as a case of severe angina pectoris. Data on cancer and mental conditions are not even included. Furthermore, the distribution of expenditures is somewhat suspect because NIH and PMA data were derived by widely differing methodologies. One major distinction worth noting is the relative emphasis on basic research. Many of the NIH branches have major programs in the basic sciences that are unmatched by industrial laboratories. The bulk of industry research spending is committed to applied research and development costs.

Federal spending on R&D for acquired immunodeficiency syndrome (AIDS) continues to grow. Total Public Health Service support in 1987 is estimated to have been \$415 million, up 78 percent from the previous year.⁹ The NIH component in 1987 was \$253 million, up 87 percent. Most of the major pharmaceutical firms and medical biotechnology companies have announced projects for AIDS diagnosis or therapy.

Innovation And The Product Life Cycle

Innovation in the *techniques* of drug discovery is occurring at a rapid rate. Older strategies of synthesizing thousands of compounds and screening for activity are being supplanted by detailed studies of the mechanism of drug action. Knowledge regarding cell surface receptors has been especially fruitful. Scientists are hopeful not only that the new biotechnologies will allow large-scale production of natural biological compounds such as growth hormone and TPA, the blood clot dissolver, but that the new genetic and immunologic tools will yield further insights into the molecular basis of disease. According to this scenario, chemists then can design simpler, easy-to-administer compounds with highly specific effects.

After the discovery phase, candidate compounds are put through extensive feasibility tests, which principally rely on experiments in animals. This work typically takes a year, with patent applications usually filed early in the process. Subsequent development is marked by regulatory milestones, beginning with the filing of an investigatory new drug (IND) application at the FDA. An IND is required at the point where human testing first begins.. In Phase I of human trials, drugs are given carefully to a few healthy subjects to learn about distribution, elimination, and toxicity. Then, in Phase II, dose-finding studies are performed in a small number of people with the condition for which the drug is intended. Finally, Phase III clinical trials involve larger populations of people similar to those who will use the drug after approval. Here, further toxicity data is accumulated, but efficacy is the key concern.

Although the clinical work often requires more time than any other part of drug development, drug companies report that clinical trials account for only 22.7 percent of R&D costs.¹⁰ Records from all of these animal and human studies then are assembled in a data package, along with detailed plans showing how the company proposes to manufacture the product. This constitutes a new drug application (NDA).

The process of innovation for medical devices proceeds somewhat differently. Progress in engineering may be more incremental than that in chemistry. Every now and then, breakthrough products appear, but most innovation emerges as a steady stream of improvements to existing technologies. The regulatory process for new medical devices parallels that for drugs, with the exception that many devices are regulated as variations on older technology and can be approved quickly under a process known as 510k review. Requirements are graduated according to product classes, with the least regulation affecting Class I products such as tongue depressors. More attention is given to x-ray devices and related

products in Class II. Breakthrough technology in any class, and particularly products in Class III such as pacemakers and artificial implants, are more likely to require filing of an investigational device exemption (IDE) to notify the FDA that human trials are contemplated. If these trials are successful, a premarket approval (PMA) application follows.

Patents

Since 1976, new drugs and medicines have been patented in the U.S. at a fairly constant rate averaging 2,233 per year.¹¹ The trend is toward increasing foreign ownership. In 1986, 44 percent of the drug patents were issued to foreign corporations and 41 percent to U.S. companies. However, U.S. companies still dominate patenting activity in the medical device arena. Of the 3,228 patents issued in 1986, only 28 percent were issued to foreign owners.¹² A greater percentage (35 percent), however, of the 1,220 patents classified by the Health Industry Manufacturers Association (HIMA) as being for "high-technology" products went to foreign owners.

Patents in the area of biotechnology are increasing rapidly, up 20 percent in 1987 to 1,476.¹³ Only 845 (57.2 percent) of these were directly related to pharmaceuticals or health care, however. In this area, U.S. industry still holds an edge over foreign competition, owning 37.6 percent of the patents compared to 23.8 percent by foreign corporations. U.S. universities own 11.7 percent of the health-related biotechnology patents, and 9 percent are owned by U.S. nonprofit institutions. The U.S. government owns only 2.2 percent, compared to 2.6 percent for foreign governments.

To the Patent Office, biotechnology means the use of microorganisms, cells, or enzymes to obtain a desirable transformation. Since this also includes the many variations on fermentation processes, only a portion of these patents were issued for the types of genetic engineering techniques considered to represent the "new biotechnology." In 1987, 207 biotechnology patents were actually for genetic engineering techniques.¹⁴ These were divided among recombinant DNA (40 percent), hybridoma technology (29 percent), monoclonal antibodies (26 percent), and DNA probes (5 percent).

Successful biotechnology R&D is not limited to the exotic companies created in the past fifteen years. Patent data supports claims made by industry sources that large, well-established pharmaceutical companies are actually outspending the glamorous biotech start-ups in this area by severalfold. The prevalence of patent litigation is also striking (Exhibit 5). This may be due to the rapidity with which ideas are being introduced to

Exhibit 5**Patent Suits In The Biotechnology Industry**

Plaintiff	Defendant	Drug
Genentech	Abbott Laboratories	Activase ^p
Genentech	Invitron	Activase
Genentech	Toyobo	Activase
Genentech	Lilly	Growth hormone
Wellcome plc	Genentech	Activase
Eli Lilly	Genentech	Growth hormone
Roche	Genentech	Growth hormone
Amgen	Genetics Institute	EPO ^b
Amgen	Chugai Pharmaceuticals	EPO
Genetics Institute	Amgen	EPO
Amgen	Cetus	IL-2c
Cetus	Amgen	IL-2
Amgen	Integrated Genetics	EPO
Centocor	Cetus	Septic shock M-Ab's ^d
Cetus	Centocor	Septic shock M-Ab's
Scripps/Rorer	Genentech	Factor 8
Scripps/Rorer	Baxter	Factor 8
Enzo Biochem	Johnson & Johnson	DNA probes
Hybritech/Lilly	Abbott Laboratories	M-Ab assays

Source: Jeffrey R. Swan, *Biotechnology Industry Focus*, Goldman Sachs & Co., March 25, 1988.

^a Tissue plasminogen activator (TPA).

^b Erythropoiten, a blood cell growth factor.

^c InterleukinZ, an immunomodulator.

^d Monoclonal antibodies.

practice, the number of new entrants into the field, and the lack of precedent for certain novel forms of intellectual property.

Regulatory Filings And Approvals

Exhibit 6 is a record of drug and device filings since 1980. Only a fraction of approvals are for novel drugs, new molecular entities (NMEs). In 1987, twenty-one novel compounds were approved, including highly publicized products such as TPA, lovastatin to reduce cholesterol, and AZT for AIDS and AIDS-related complex (ARC).¹⁵ Less attention has been given to approvals for fluoxetine, a new antidepressant; a purified form of Factor VIII for hemophiliacs; three new antibiotics; new drugs for cancer, hypertension, and heart failure; and five new diagnostic products. Major devices cleared for marketing in 1987 include the first synthetic ligament (for use in knee surgery); an anti-tachycardia implantable pace-maker; the first fiberoptic laser device to remove fatty deposits in large

Exhibit 6
Regulatory Filings And Approvals, 1980-1987

Year	Drugs				Devices			
	INDs ^a	NDAAs ^b	NMEs ^c	Suppl ^d	IDEs ^e	PMAAs ^f	Suppl ^d	510ks
1980	1,087	114	12	3,812	63	24	78	2,908
1981	1,184	96	27	3,735	232	32	239	3,381
1982	1,467	116	28	3,626	189	49	238	3,256
1983	1,798	94	14	2,873	187	46	327	3,162
1984	2,112	142	22	3,593	198	43	243	4,262
1985	1,623	100	30	3,354	201	37	377	5,095
1986	1,087	98	20	3,403	213	72	477	5,359
1987	- g	- g	21	- g	224	46	565	4,992

Source: Food and Drug Administration, *New Drug Evaluation: Statistical Report*, NTIS PB87-195335 (Rockville, Md.: FDA, April 1987); Pharmaceutical Manufacturers Association; and FDA, Office of Device Evaluation, Center for Devices and Radiologic Health, Annual Report, Fiscal Year 1987.

^a Investigatory new drug applications.

^b New drug applications.

^c New molecular entities.

^d Supplemental applications.

^e Investigational device exemptions.

^f Premarket approval.

^g Data not available.

arteries; and the first opaque tinted contact lenses.¹⁶

The FDA is proud of the fact that AZT was approved in just three and a half months and lovastatin in just nine and a half months. With these dramatic exceptions, however, 1987 drug approvals offer little evidence that the review process has accelerated. Approval time for all NMEs averaged 32.3 months, almost exactly equal to the average of the five preceding years.¹⁷ The Center for the Study of Drug Development examined approvals for 1985-1986 in more detail.¹⁸ The mean length of the IND phase of development was 5.6 years for compounds other than orphan drugs. Combined with an average 2.6 years in the NDA phase, these drugs required 8.2 years from IND filing to approval for marketing. Development and review times varied with therapeutic class: psychopharmacologic agents required almost twice as many years in development and review as anti-infective agents.

Medical devices gain approval much faster, perhaps related to the incremental nature of device innovation. In 1987, approval of 510ks averaged sixty-nine days; PMAs took an average of 337 days.¹⁹ In some cases, the time spent waiting for reimbursement approvals is more of a factor in return on investment calculations for medical devices. Cochlear implants for hearing loss and magnetic resonance imaging (MRI) required twenty and forty-two months, respectively, before being approved for Medicare reimbursement.²⁰

Regulatory delay has a major impact on the balance of incentives for industry to invest in R&D. The out-of-pocket cost for developing a new drug was estimated as \$65 million in 1986 dollars.²¹ When the opportunity cost of this investment is considered using an interest rate of 8 percent, a new drug can be considered to carry a price tag of \$125 million. Based on these estimates, the savings produced by shaving only one month off the approval process is about \$800,000.

Recently, the FDA has launched a number of regulatory innovations in an attempt to reduce delays. The deputy commissioner points out that the backlog of unapproved NDAs was at a ten-year low at the end of last fiscal year.²² Similar progress has been made with PMAs and supplements. He argues that progress on these backlogs paradoxically inflates the current average approval time. Provision for submission of NDA data in computer-readable formats (electronic NDAs) may lead to faster, and even more thorough, review. The thought is that instead of asking companies to provide follow-up analyses, FDA reviewers can use their own computers to scrutinize data in new ways. The commissioner also has exhorted companies to improve the quality and reviewability of their submissions.²³ New procedures have been established for "treatment INDs" meant to facilitate early availability of experimental drugs for life-threatening conditions by allowing companies to charge for their use. New expertise in the field of epidemiology also has upgraded the agency's capabilities.

Only a fraction of drugs for which an IND is filed successfully obtain NDA approval. In the ten years preceding 1987, NDA approvals represented only 7.2 percent of the INDs filed during that period. For devices, PMA approvals represent only one-quarter of the number of IDEs filed since 1980. For both drugs and devices, supplemental applications are used to request approval for changes in minor product details, manufacturing practices, and, in some cases, the information provided to users. Devices used in radiology and cardiovascular applications have especially high ratios of supplements to PMAs (2.8 and 1.7, respectively) compared to those used in microbiology (0.24), suggesting that innovation in these areas is taking place in an especially incremental (evolutionary) fashion, rather than in large breakthrough steps. This may also reflect the fact that the information component (or "software") in medical products is being given increasing attention as a way to increase the value of therapy.

Sales Growth

Changes in sales figures provide a final perspective on health care innovation. The U.S. research-based pharmaceutical industry reports

that worldwide sales grew 11 percent to \$41.2 billion in 1986.²⁴ U.S. sales of human pharmaceuticals grew 12.3 percent to \$28.3 billion. Since absolute prescription numbers were virtually flat, a gain means that the average price per prescription rose.²⁵ This increment reflects both the increased prices for old products and the substitution of higher-priced, innovative products for older drugs. The medical device industry expects to ship \$22.5 billion in goods in 1988, up 8 percent from 1987.²⁶

Competition

Medicare's prospective payment system (PPS) may have had more impact on the medical device industry than on drug companies so far. Most big-ticket devices are used in hospital settings where price competition is growing fierce. According to the Commerce Department, manufacturers' prices rose only 2 percent in 1986 and 1987, compared to 9.1 percent in 1985.²⁷ The industry has responded by consolidating product lines, eliminating unprofitable operations, and designing products thought to be more cost-effective. Examples include miniaturization of plastic disposables and a resurgence in reusable products. Device industry structure is related to product sophistication. Typically, thirteen companies manufacture a single Class I device, an average of eight companies make each Class II product, and only four and a half manufacturers produce a given Class III device.²⁸

Hospital pharmacy and therapeutics committees now scrutinize drug budgets carefully and use innovative policies to keep costs down. Therapeutic substitution, for example, is more aggressive than the automatic substitution of chemically identical generic compounds for brand-name drugs. Therapeutic substitution policies allow pharmacists to substitute a drug from an entirely different chemical class for certain specified indications. The U.S. pharmaceutical industry is also characterized by vigorous competition in most therapeutic areas. The four largest firms account for only 25 percent of sales; the top eight account for less than half of sales; and no firm has more than 7 percent of the overall market.²⁹

Domestic drug and medical device manufacturers hang onto a positive balance of trade with foreign countries. In 1986, the trade surplus for pharmaceuticals was \$764 million. This gap has narrowed since 1980. Devices register a positive balance of trade overall, but there is a deficit with respect to West Germany and Japan.³⁰

The authors wish to acknowledge the assistance of Jane White at Health Affairs and Gary Persinger of the Pharmaceutical Manufacturers Association in locating information for this DataWatch.

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