

HUMIC ACID

FACTS AND FIGURES OF INTEREST



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The Pharmaceutical Industry

The entrepreneurial spirit was something that existed in pharma in the 1980s, in their heyday, but it's hard to find now because such companies have become so big and risk-averse (42).

Research pipelines at big pharmaceutical companies, directed at overserved therapeutic categories, are running dry, and the sector may be hitting the limit on growth through consolidation as well. "Big pharma" is, in fact, today so big that the scramble to maintain double-digit growth now works against any effort to jump-start innovation. Projects are dropped unless they are deemed certain to produce drugs with sales of a billion dollars, and research budgets are cut as major pharmaceutical companies turn to tweaking their breadbasket products in hopes of gaining brief patent extensions (42).

There is a growing tension between the development of small-molecule and large-molecule therapies—between the pharmaceutical industry's traditional synthetic organic chemicals and the complex proteins and antibodies that are emerging from biotechnology (42).

What distinguishes biotech companies from big drug companies is that the former are biology-driven whereas the latter are primarily chemistry-driven (42).

In most cases, industrial biotechnology is not limited by technology, but by the size and resources of companies doing the research (91).

It is estimated that about 30% of the drugs in the development pipeline are biopharmaceuticals—the majority at preclinical stages. The question is: how many of these candidates will make it to commercial launch. Industry watchers predict that the 40% failure rate for small-molecule drug candidates in late-stage clinical trials will probably translate into a similarly bleak prospect for success in biotech drugs (42).

The mounting banks of targets for new biotech-derived drugs have created an enormous new opportunity for growth. The expanding role of biology vis-à-vis the human genome has, however, introduced uncertainty as to which sector of the industry—major pharmaceutical or biopharmaceutical—will benefit most (42).

From their small base—currently 8% of the \$390B worldwide drug market—biopharmaceuticals are expected to reach 15% of a \$550B market by 2006. Nevertheless, the state of the industry is such that large pharmaceutical companies are driving what is going on, and they are (and are likely to continue to be) skewed toward small molecules due, if nothing else, to their much-cheaper cost of production (42).

In march 2003, the healthcare industry was estimated to be \$1.4 trillion, amounting to nearly 15% of the U.S. gross domestic product (356).

Industry Trends

Despite consolidation since 1999, the pharmaceutical market remains fragmented. For example, Pfizer had the lead position in 2001 with \$26 billion in sales and a 7.0% market share; in 1998, Merck held the top slot with \$15 billion in revenues and a 7.6% market share. With the acquisition of Pharmacia, Pfizer's market share will jump to about 11% (187).

In the future, the pharmaceutical industry will in all likelihood be dominated by a handful of marketing-oriented behemoths. The top 10 companies today (2002) already control over 47% of the pharmaceutical market (at year-end 2000: Pfizer—7.1% global market share, Glaxo SmithKline—6.9%, Merck—5.1%, AstraZeneca—4.4%, Bristol-Myers Squibb—4.1%, Novartis—3.9%, Johnson & Johnson—3.9%, Aventis—3.6%, Pharmacia—3.2%, and American Home Products—2.6%) (17).

With global R&D spending outpacing the rate of global sales growth, and patent expirations outpacing new chemical entity approvals, the pharmaceutical industry is feeling tremendous pressure to improve new-drug pipelines and productivity (33).

Major pharmaceutical companies are facing difficulties in 2002 and beyond: patents on \$100 billion worth of drugs are expiring over the next several years; the time and cost of bringing a new drug to market continue to rise; and investors are holding companies to annual sales and earnings percentage growth in the mid-teens per year which, for the average company with \$20 billion in annual sales, means launching products that will bring in another \$3 billion each year (166).

Mega-mergers of big pharma are likely to continue into the future in light of the increasing sales and marketing muscle needed to give new drugs a successful launch and then maintain their market share (17).

Many major drug producers have undergone massive mergers to find cost savings and critical mass in R&D and marketing in recent years. They also strive to grow organically through the internal discovery and development of new products and, to complement or accelerate these efforts, they often look to small technology-based companies for capabilities or potential new drugs (166).

While R&D spending in general is expected to increase, the future of R&D at big pharma companies is in question. Many believe that such companies will eventually do relatively little of their own R&D, instead licensing compounds for sale from smaller, specialized niche pharmaceutical firms or biotechnology companies (17).

There were two particularly striking trends in the pharmaceuticals industry in 2002: the dominance of product-based deals and the number of private equity-backed acquisitions (e.g., Advent International's acquisition of Viatris from Degussa for about \$350 million, and the \$1.13 billion purchase of Nycomed led by CSFB Private Equity) (187).

As large drug makers focus on medicines with blockbuster potential, many are transferring niche projects from their development portfolios to other companies, in a bid to wring some value from their research investments. For example, in March 2003 Glaxo SmithKline shed an experimental antibiotic research program in exchange for a stake in Affinium Pharmaceuticals, a closely held biotechnology concern in Toronto: Glaxo transferred patents, technology, and marketing rights for a program to develop an antibiotic against staphylococcal infections caused by drug resistant bacteria—a rising medical problem—to Affinium in exchange for a significant equity stake in Affinium and a seat on its board (172).

The chemical industry is moving away from a traditional R&D focus on a few long-term projects toward managing a roster of many smaller ventures with smaller potential payoffs in biotech work (91).

When few new drugs are launched, big custom manufacturers of advanced intermediates and active drug ingredients are hit badly, as they were in 2002. But because research in pharmaceutical companies must go on—to discover new drugs and feed the development pipeline—providers of exclusive synthesis for the early phases of drug development fared better than custom manufacturers in 2002. Business, though slower, allowed gains over the previous year and the expansion of operations. The outlook for 2003 is optimistic (191).

The custom pharmaceutical chemicals industry is in a downturn thus far in 2003, and many observers don't see substantial growth returning until 2004 or beyond (189).

Small-molecule custom drug manufacturing is an \$8B market growing at 6 to 8% annually. Microbial and mammalian cell biologics drug production, in contrast, is a \$1.5B market growing at 15 to 20%. The small-molecule piece of the pharmaceutical industry is therefore likely to remain the largest segment for the foreseeable future—even 10 years out (42).

Supply-side as well as demand-side factors promise to lift biotech firms in the years ahead (158).

Major drug makers see “branded generics” eating into profits; altered copies outmaneuver patents in legal battles, boosting market pressure (351).

Mergers and Acquisitions

Analysis of 12 major mergers and acquisitions from 1970 to 1996 shows that market share declined—ranging from as little as 6% to as much as 53%—following the merger. In contrast, six major pharmaceutical companies that did not merge posted market share increases ranging from 11 to 110% from 1990 to 1996 (33).

A total of 567 pharmaceutical and biotechnology alliances were signed between January and July 1999. The types of deals included disease management, comarketing, copromotion, equity investment, product swap, joint venture, manufacturing, marketing and licensing, product acquisition, and R&D contracting.

More than 90% of all alliances were for early-stage R&D projects; the number of alliances for late-stage development candidates and commercial products is, however, on the rise (33).

Although the pharmaceutical industry did well in 1999, it wasn't good enough to prevent another round of consolidations (33).

A scarcity of potential blockbuster drugs in drug makers' research pipeline spurred merger fever in the pharmaceutical industry in 1999 (5).

Commitments to research alliances hit \$5.3B in 1999, triple the 1994 level. For example, the proportion of Bristol-Myers' research budget that is spent on research alliances with biotechs is up to almost 30%. At Warner-Lambert, money spent on alliance research rose from nothing five years prior to 25% of the budget in 1999 (8).

The increasing inefficiency of in-house R&D in bringing new drugs to market has led drug-company executives in 2000 to pour money into buying and teaming up with independent production companies (8).

In contrast to "big pharma", by the beginning of 2002 more than 300 biotechnology product candidates were in late-stage clinical development—where the success rate runs about 80%—with more than 50 products awaiting regulatory approval. Many biotech companies were also flush with cash from product sales, collaborative R&D funding, and recent stock market prosperity. From these positions of strength, biotech companies grew through acquisitions and by using their leverage to strike more lucrative and constructive partnerships with other biotech or big drug partners. For example, in the last 29 days of 2001, biotech companies initiated \$20 billion in acquisitions (however, while the total value of transactions doubled in 2001, the number of deals actually fell) (166).

Recent examples of the collaboration between pharmaceutical firms to help fill drug pipelines include development and commercialization deals between Eli Lilly and Amylin (\$325M to Amylin in up-front and milestone payments), and between Roche and Kosan Biosciences (\$220M to Kosan in milestone payments) (15,16).

Twelve pharmaceutical company partnerships were announced in the second quarter of 2002, a 100% increase over the previous quarter (15).

Trends in today's biotech industry include a stronger focus on sustainable business models centered on product development rather than sexy technologies; and thinking more about creating critical mass and greater value through mergers and acquisitions—a trend that's expected to continue through 2003 (38).

The value of overall U.S. corporate merger and acquisition (M&A) activity dropped in 2002 by as much as 40 to 50% compared with the boom years of the mid- to late-1990s. M&A in the drug sector, however, soared to a record 45 in 2002, although the total dollar amount fell to a four-year low of \$26.4 billion (almost 60% of which was the \$15.4 billion combination of biopharmaceutical firms Amgen and Immunex, which created a clear leader in that sector with 2002 sales of \$5.23 billion and net earnings of \$1.66 billion). There was a distinct absence of multi-billion-dollar

mergers between large traditional drug producers in 2002 as well, unlike in 2000 when several big combinations boosted the total to \$233 billion (187).

U.S. drug companies were responsible for most of the company acquisition activity in 2002, usually buying U.S.-based targets. However, activity also picked up in Europe and in the Asia-Pacific region. Twenty-one deals were completed in Europe, up from just six in 2001 and 11 the year before. In Asia and elsewhere just six were completed in 2002, about average for the previous four years (187).

Although limited in number, the acquisition activity in Asia was significant in 2002, and is likely to continue, especially at the smaller end of the M&A spectrum (187).

In total, counting those valued above \$25 million each, there were 18 biotechnology M&A completed in 2002, worth a combined \$5.2 billion (although two deals accounted for most of it), up from 13 the previous year that totaled just \$1.6 billion. There has also been a recent upsurge of consolidation activity in the European biotech sector (187).

The year 2003 began with new collaborative alliances of small drug discovery companies with larger drug development partners (1).

Pharmaceutical companies continued in 2003 to target biotechnology companies for M&A, particularly the lower-risk, limited subset of biotech companies with products on the market or in late-stage development. Such acquisitions have accounted for a significant fraction of deals in recent years (187).

Pharmaceutical companies can save anywhere from 30 to 40% of an acquired company's cost base, mostly through the elimination of overlapping products, functions, and overhead expenses (33).

Many believe that synergies between the R&D departments of two merged companies rarely result in increased numbers of new molecular entities being brought to market. Rather, mergers are good substitutes for R&D productivity only if the latter is missing (33).

There is growing skepticism that mergers will lead to replenished new-drug pipelines. For example, since Glaxo Wellcome merged with SmithKline in December 2000, GSK has not launched one significant new product (17).

In such tough financing environments, partnerships of biotech companies with larger drug firms have usually been a given. However, that's not necessarily true today, analysts say, and conditions are even more challenging because the pharmaceutical industry itself is in a weakened state and undergoing restructuring (38).

Despite an apparent lack of benefit, analysts nonetheless believe that the pharmaceutical industry's consolidation will continue as long as the financial community expects continuing high rates of return (33).

There is compelling reason for consolidation within the biotech industry, primarily the collapse of biotech stocks after mid-2000 and the difficulty since then of locating

financing. Some observers feel there are too many biotech companies with too little cash, too few products, not much management, no critical mass, and definitely no revenue, which will continue to drive consolidation well into the future (187).

The importance of partnerships between large chemical firms and agricultural or biotech firms is likely to continue (91).

Several factors are driving drug industry consolidation: patent expirations, generic competition, high R&D costs, increased competition, manufacturing issues, regulatory problems, and product setbacks. The bottom line comes down to the need to expand product pipelines and the desire to realize cost savings and greater R&D productivity through mergers (187).

One reason for the increase in industry mergers is that the industry's ability to come up with new drugs is not keeping up with the attrition of products going off patent (8).

Partnership is an important route for drug firms that lack a biopharmaceutical infrastructure (42).

Realization of bigger, better R&D continues to be cited as one of the main reasons for big-pharma mergers and acquisitions (17).

Long-term investment is increasingly going to the entrepreneurial companies in biotechnology. Chemical companies will therefore need to form partnerships with these companies or risk having to become low-cost producers of traditional materials (91).

The pharmaceutical copromotion deal has emerged as a popular strategic alternative between the one extreme of trying to expand a company purely through organic (i.e., in-house) means and the other extreme of merging with, or acquiring, another company (33).

Small drug-discovery firms continue to find collaborative opportunities with larger development partners (43).

Biopharmaceutical companies are finding new strength through partnerships with big drug companies. However, biotech companies don't feel they have to knuckle under when they get offered a deal by big pharma. By 2010, the two groups will in fact be launching the same number of products each year. The products won't be the same value but, given its size, biotech doesn't need them to be (42).

Schering-Plough Corp.'s new CEO, Fred Hassan, rejected suggestions that the struggling company would seek a merger with Merck & Co., saying that would be an "easy way out" but not the best way to maximize value for Schering-Plough's shareholders (348).

In the wake of Pfizer's \$57 billion acquisition of Pharmacia earlier in April, the company said it would shutter three of 25 major R&D centers around the world and shuffle many functions among the surviving facilities, in efforts at rapidly

integrating the operations of Pharmacia as well as enhance Pfizer's ability to discover new medicines (349).

Consolidation continues in the British biotechnology industry. British Biotech, once the sector's star, has agreed to merge with privately held RiboTargets in a deal that values RiboTargets at about \$40 million, creating a company with a market capitalization of roughly \$80 million and a cash reserve of nearly \$70 million (352).

Biotech companies receive a larger share of all venture-capital investments in 2002—13.2%—than they did during any of the previous six years. However, investments in biotech companies slipped for the second year in a row, to \$2.8 billion—well off the peak of \$4.4 billion invested in 2000 (354).

Pfizer and Pharmacia are on course to complete their merger in May. The companies recently agreed with the FTC on required divestitures. European regulators gave their conditional blessing in late February (355).

Companies

Typical of big pharma, sales of Johnson & Johnson's top seven drugs grew from 1998 at a compound rate of 26% a year. But the portfolio is showing its age and sales growth for these specific medicines will slow to 12% in 2003, and to 9% in 2004. Absent major acquisitions, total pharmaceuticals sales growth will in fact slip to 8% to 9% annually beginning in 2003, from about 15% growth in 2002. Slower growth is a major challenge because 60% of Johnson & Johnson's operating profits come from pharmaceuticals sales, which were \$17.2B in 2002, or 47% of total revenue (39).

Johnson & Johnson is expected to take over money-losing Scios, which sells a new drug for heart failure called Natrecor. However, there are industry doubts about Natrecor's growth prospects, cost effectiveness, and safety (94).

In efforts at filling its sparse pipeline for new drug development (which holds few immediate prospects), Johnson & Johnson is in talks to buy biotechnology concern Scios, Inc—a 23-year-old unprofitable biotechnology company that sells one drug and is developing another—for about \$2B (39).

Johnson & Johnson has agreed to pay about \$2.4 billion in cash to acquire Scios, an unprofitable biotechnology firm with one product on the market—natrecor, regarding which there have been some safety concerns (192).

The FTC approved Johnson & Johnson's \$2.4 billion acquisition of Scios. The deal is expected to close following a Scios shareholder vote on April 28 (353).

In 1997, Glaxo SmithKline paid LG a \$38M up-front fee for the international rights to gemifloxacin. Additional royalty payments to LG could have been worth several hundred million dollars (13).

Glaxo Wellcome and SmithKline Beecham approved a merger of the two companies, which would create Glaxo SmithKline with about \$27 billion in annual sales. The merger is scheduled for completion by September 25, 2000 (165).

The Glaxo-Wellcome/SmithKline Beecham merger, worth \$71B, was expected to be completed by August 21, 2000. The new company, Glaxo SmithKline, will be the world's largest drug maker, with combined annual sales in 1999 of \$27.2B and a pooled sales and marketing force of 43,000 worldwide (34).

The pharmaceuticals industry spate of mergers continued as Glaxo Wellcome and SmithKline Beecham agreed to a megamerger in a \$76B stock deal that created one of the world's top-five pharmaceutical companies. The companies cited many reasons for the merger, including a rapidly changing industry, patent expirations on key products, and the need to build a critical mass in R&D to bring new pharmaceuticals to market (30).

Glaxo Wellcome's announced acquisition of SmithKline Beecham is the latest pairing in the drug industry. The trend to consolidate has been accelerating with yesterday's deal coming just four weeks after the announced merger between Monsanto Co. and Pharmacia & Upjohn (36).

From 2003, over the next five years Glaxo SmithKline faces either patent expiration or potential competition from generic makers of six of its major drugs. Glaxo hopes to compensate by marketing drugs discovered by other companies and by launching product extensions on existing products. However, neither approach provides the high margins necessary to sustain a company the size of Glaxo, which had overall sales of \$28.5 billion in 2002 (177).

Two years ago, Glaxo SmithKline embarked on an unusual effort to make its drug-discovery process more efficient by mimicking smaller, nimbler biotechnology firms. In the crucial middle stage of drug discovery—in which scientists must decide whether to take a particular compound into large-scale tests or to discard it entirely—Glaxo has dispensed with a traditional hierarchical structure. Instead, the British company has created six “Centers for Excellence in Drug Discovery”, each focused on a separate therapeutic area. The six centers, each with no more than 350 scientists, compete against one another for resources, and their scientists can reap financial rewards, including a share of royalties, if drugs they have backed end up on the market (234).

After merging with Warner-Lambert, Pfizer will have revenue in 2000 of about \$31B and a research budget of about \$4.7B. In order to continue growing at double-digit levels, the company by 2003 will need to be launching at least three or four drugs a year that can do at least \$1B in annual sales. By 2007, when some of Pfizer's key patents expire, the company will need to launch five or six huge-selling new drugs each year. Pfizer's own labs have come up with just seven drugs in the past 10 years (8).

Pfizer is in a \$55 billion deal to acquire Pharmacia, which is expected to close this quarter (93).

Pfizer and Pharmacia are on course to complete their merger in May. The companies recently agreed with the FTC on required divestitures. European regulators gave their conditional blessing in late February (355).

R&D spending at Pfizer is expected to rise to over \$7B in 2003, up from \$4.8B in 2002 (17).

Pfizer remained the percentage leader in worldwide pharmaceutical sales at 7.3%, followed by Glaxo SmithKline at 7.1% and Merck at 5.1% (236).

As of April 30, Pfizer is the world's largest pharmaceuticals company (349).

Pfizer is overhauling R&D operations in a move to cut costs and improve efficiency (349).

Bristol-Myers Squibb launched ambitious goals for expanding its business and R&D efforts in 1997, desiring to double the number of new drugs it discovers and products it launches. To do so, it will increase its total R&D staff by 50%, to about 6,000 people over the next five years. About 1,000 scientists were engaged in drug discovery activities, and this group is expected to also double in size (31).

Zeneca presented a five-year pharmaceutical R&D plan that is aimed at doubling its research output. To meet that growth target, a bigger product pipeline will be needed, to be fueled largely by in-house research. In 1996, Zeneca's drug business spent about 16% of its \$4.1B in sales on R&D (31).

Promising products boost prices being paid for small drug development firms. Millennium will acquire Cor Therapeutics for \$2.0B in stock by year-end 2001. Millennium has made four acquisitions of smaller drug discovery firms over the past four years. In related deals, MedImmune will acquire Aviron; Cephalon will pay \$450M in cash for French drugmaker Group Lafon (10).

Onyx Pharmaceuticals is codeveloping a small-molecule cancer drug with Bayer and expects to receive a \$15 million loan from its partner, triggered by the start of clinical trials (92).

In the beginning of 2003, Theravance (a small drug discovery company) signed a deal worth up to \$545M with GSK. GSK will pay \$50M in up-front fees and for preferred stock, plus milestone payments (1).

In the beginning of 2003, Skye Pharma licensed two products to Endo Pharmaceuticals for up to \$120M in fees and potential milestone payments (1).

In the beginning of 2003, Sunesis and Biogen will work together on oral therapeutics. Biogen will pay fees to Sunesis totaling up to \$60M per disease target (1).

In the beginning of 2003, Pfizer set up a pharmacogenomics collaboration with CuraGen. Financial terms were not disclosed (1).

Biotechnology concerns Enzon Pharmaceuticals, Inc. and NPS Pharmaceuticals, Inc. are in discussions to merge, a deal that would continue a recent wave of consolidation in the biotech sector (156).

NPS Pharmaceuticals, Inc. agreed to pay \$571 million in stock for Enzon Pharmaceuticals, Inc. in a move to create a biotechnology company with a balance between medicines on the market and drugs in development. Enzon (Bridgewater, NJ) is a profitable specialty-drug maker with a weak pipeline. Its centerpiece is a technology called pegylation, which can reduce the frequency of injection and side effects of some drugs. NPS (Salt Lake City, UT) has a strong drug-research program but has never turned a profit. The agreement is billed as a merger of equals, and is the latest sign of consolidation in the biotech sector (153).

NPS Pharmaceuticals and Enzon Pharmaceuticals have agreed to merge in a stock-for-stock transaction expected to close in June 2003, creating a new company with a market capitalization of about \$1.6 billion (190).

With 2002 revenues of about \$340 million, Genencor, the 10th largest biotech company worldwide, has experienced compound annual growth of about 14% over 10 years (91).

Schering-Plough Corp.'s new CEO, Fred Hassan, rejected suggestions that the struggling company would seek a merger with Merck & Co., saying that would be an "easy way out" but not the best way to maximize value for Schering-Plough's shareholders (348).

Financials

Biotech companies, which have always relied on outside money to support R&D until they become self-sustaining, raised more than \$10B in 2002, making it the fourth most prosperous year ever for industry financing (38).

A bright spot for the biotech industry was that venture-capital spending in 2002 was up 12% to \$2.7B (38).

In 2002, biotech companies attracted just \$2.8 billion in venture capital, down from \$4.6 billion in 2000 (158).

On the surface, cash flow into the biotech industry looks great, but further inspection proves otherwise. Debt offerings were on the rise in 2002, but private and public investment declined. Stock offerings in 2002 brought in half as much as in the previous year and just 7% of what was raised in 2000. In that record year, \$32B poured in (38).

By the end of 2002, the biotech industry's market capitalization was off at least 40% from the start of the year and off more than 50% from its 2000 high. Consequently, biotech companies have been unable to turn to the stock market to raise money: in 2002, only three companies had initial public offerings (IPOs), compared with 67 in 2000 (38).

In the second half of 2002 and early 2003, about half a dozen companies went bankrupt and shut their doors, nearly as many as had in the past 20 years (38).

Macroeconomic factors, rather than sector-specific issues have lately depressed biotech stock values the most: larger market trends beyond the industry's control are driving investment behaviour, leading to lower trading volumes and money being pulled out of the market, particularly from higher risk investments such as biotech (38).

Currently in 2003, nearly 40% of biotech companies have stock values below \$2.00 per share, and 20% have values below \$1.00 a share and face delisting. Some 25% of companies are trading at a value less than their available cash per share. And many have less than a year's worth of money to fund operations (38).

Biotech companies are falling into different camps in 2003—the “haves” with product sales or capital reserves left over from the 2000 financing bubble, and the cash-starved “have-nots” looking for financing. However, even the successful or more financially comfortable companies are paring down operations to conserve resources, because the general expectation is that a recovery will not occur until 2004 or beyond (38).

Although pharmaceutical company stock values and price-to-earnings ratios have been falling, even hitting five-year lows in 2002, acquisition multiples on average have risen. After slipping in 2001 and 2002, multiples in 2003 now average about 20 times EBIT (earnings before interest and taxes) and fall in a very broad range from about 5 to 50 (187).

New products and expanded sales boosted the biotech sector's 30 top companies' combined 2002 fourth-quarter revenues by 21.7% to \$7.01 billion. But R&D and other expenses contributed to an overall 3.8% decline in earnings to \$849 million. Revenues for 2002 rose 19.0% to \$24.3 billion, while earnings fell 7.3% to \$3.14 billion (235).

Combined 2002 fourth-quarter sales for the 17 largest global pharmaceutical producers rose to \$82.0 billion, up 8.0% compared with the same period last year. Overall earnings for the 15 companies reporting quarterly results gained 11.6% to reach \$14.8 billion. However, poorer performance in earlier quarters cut into gains for the year—sales for the entire group were up just 6.2% to \$304 billion and earnings also rose 5.9% to \$61.8 billion (236).

After years of restraint, drug makers are pushing up U.S. prices on some of their most important medicines. That's a worrisome development for consumers, employers and the government (350).

New Drug Development

The U.S. pharmaceutical industry leads the world in drug discoveries, with 45% of the prescription medicines marketed worldwide in the 1990s developed in the United States (U.K., 14%; France, less than 5%) (7).

U.S. Pharmaceutical industry's production of breakthrough medicines—the products vital to propelling revenues and profits over the next decade—has actually declined since 1996. The industry is therefore becoming increasingly reliant on costly marketing schemes, and relatively less on its research operations (8).

Drug makers in the U.S. launched just 17 new drugs in 2002, their worst new-product performance since 1983 and a sharp decline from the 53 new drugs launched in 1996. The dearth of new products threatens the industry's long-term future and has panicked some industry executives (154).

Drug approvals were a bright spot for the biotech sector in 2002: the FDA approved 20 new biotech products during the year, about half of which were therapeutics. Another 370 drugs are in late-stage development (235).

New Drug Development: Costs

U.S. research pharmaceutical companies invest a higher percentage of sales in research and development than any other industry, including electronics and aerospace (7).

Drug firms will spend \$24B in 1999, or about 20% of revenue, to discover and develop new medicines (5).

In 1999, the global pharmaceutical industry increased R&D spending 14% to a record \$24B. Much of that money supported ever larger clinical development programs and funded the increasingly complex industrialization of drug discovery (33).

A drug takes 10-12 years to get through the discovery process and clinical trials at a cost of about \$500M (12).

U.S. research-based pharmaceutical companies invested more than \$26B in 2000 to discover and develop new medicines—a 10% increase over 1999 (7).

On average, in 2001 it took 12 to 15 years and more than \$500M to bring a new medicine to the marketplace (7).

The average cost in 2001 of developing a prescription drug is estimated to be \$802M in 2000 dollars. This figure includes the costs of failures as well as the opportunity cost of funds spend on R&D that could have been earning money in another investment. The average drug-development cost in 1987 was \$231M. Had costs risen along with inflation, the average cost of drug development would be \$318M in 2000, less than half of the current estimate (11).

At year-end 2001 the average cost of discovering and developing a new medicine had risen to \$802 million, with an average development time of 12 years. \$403 million are out-of-pocket expenses; the rest is an estimated cost of capital—the return that investing the money at an 11% rate of return would have earned over time. Research costs have risen 2.5 times in inflation-adjusted terms since 1987, when the average research expense was \$231 million. Total research costs

increased 7.4% annually in the 1990s. Clinical costs—the component of research associated with testing drugs in humans—rose 12%. The number of patients in a new drug trial has increased from about 1,300 in the early 1980s to more than 4,000 for a typical medicine in 2001 (80).

The average cost to develop a new prescription drug was \$231 million in 1987 dollars; in 2002 the "fully capitalized resource cost" was \$802 million in 2000 dollars—a 250% increase, adjusted for inflation, over 11 years (164).

It is now estimated that each FDA-approved drug must return between \$300M and \$600M to cover the research costs of the many that don't pan out (8).

To create a 10% compounded annual return on its year-2000 \$4.7B research and development investment, Pfizer researchers will have to come up with products in 10 years that create \$12B in new revenue that tenth year (8).

New Drug Development: Indirect Costs

In 1998, Schering-Plough Corp. spent \$136M advertising just one medicine, its allergy drug Claritin (\$1.7B in U.S. sales). That's more than Coca-Cola Co. spent advertising Coke, or Anheuser-Busch Cos. spend advertising Budweiser (8).

Pharmaceutical companies generally have to test 5,000 to 10,000 compounds for each one that eventually becomes a new medicine (7).

Less than one-third of the drugs that make it to the marketplace recover their research and development costs (7).

Patents and Patent Protection

Patent protection for drugs has increased substantially over the past two decades, resulting in hefty increases in industry profits and consumer drug bills, but not necessarily in innovation (6).

From 1979 to 1989 the Patent and Trademark Office granted between 2,000 and 4,200 drug patents annually (19).

Because of the overwhelming public interest in AIDS research, the Patent and Trademark Office was pressured into establishing a separate database for AIDS-related inventions in 1994, to give other scientists access to the cutting-edge research in patents (32).

Patent protection for new medicines is essential in order for companies to recover the costs associated with discovering and developing new medicines (7).

"Effective" patent lives are the parts of patent terms remaining after drugs are approved by the Food and Drug Administration. Because of federal intellectual-property laws adopted over the past two decades, new brand-name drugs now have effective patent lives of about 13 to 15 years, compared with 8 years for drugs approved in the early 1980s (6).

As a rule of thumb, a pharmaceutical company will lose 75% of a product's sales within 24 months after losing patent exclusivity (33).

In 1999, 36 branded pharmaceutical products, representing more than \$1.9B in sales, lost patent protection, opening the doors to generic competition. Another 173 products, worth \$30B in sales, are projected to lose patent protection between 2000 and 2005 (33).

One-hundred fifty drugs with \$50B in combined annual sales will lose patent protection over the next five years (6).

In the U.S. market, drugs with annual sales of more than \$60B face patent expiration over the next decade; 13 of the leading 35 molecules will lose protection over the next five years (17).

A recent court decision has redefined patent protection for drug makers. Pharmacia and Pfizer won a victory in the U.S. District Court for the Western District of New York, which ruled invalid a University of Rochester "use" patent. "Use" patents were thought to represent a new frontier for protection of intellectual property in the drug industry. By essentially staking a claim on a method for influencing biology, this type of patent is designed to cover any medicine that acts through a particular biological pathway. The ruling is being interpreted to mean that companies (or, in this case, a university) can't use a patent on a single early stage compound (including its biological action) to block invention and development of potentially hundreds of drugs that rely on the same biological pathway (178).

Widening a campaign against companies that use regulation to gain commercial advantage, the Federal Trade Commission recently settled with Bristol-Myers Squibb for \$670 million on charges that for a decade the drug company illegally sought to extend patent protection on three blockbuster drugs, thereby blocking competition from less-costly medications and shielding more than \$2 billion in annual sales from competition by generics—forcing patients to overpay hundreds of millions of dollars for medications (180).

European Union officials have agreed on a new single patent court intended to bring down the cost of patent filing and to boost European competitiveness. The move is expected to lower the cost of filing a patent to about \$27,000. It costs a total of roughly \$50,000 today to file separately in each European country, compared with about \$10,000 in the U.S. (233).

FDA and Other Regulatory/Related Considerations

The path from initial lab work on a drug to final FDA approval is generally a 10 to 15-year process (46).

Before a drug company or research institution can submit an Investigational New Drug Application (INDA) to the Food & Drug Administration, it does an average of six-and-a-half years of basic discovery work and preclinical testing in lab animals. The INDA includes the results of the discovery work and testing in lab animals and

describes the human testing that the sponsor—a company or research institution—proposes to do. At this stage, FDA decides whether it would be reasonably safe to test the drug on humans (46).

In the first phase of clinical trials—called Phase I toxicity testing— the drug is administered to 20 to 80 healthy volunteers for about a year and a half. At this point, researchers are looking at safety and trying to determine probably safe dosages. They are also attempting to detect the most frequent side effects and to learn how the drug is metabolized and excreted (46).

Generally, out of five drugs tested in Phase I trials, only two emerge as acceptable and progress to Phase II (46).

If the results of Phase I trials indicate acceptable toxicity, Phase II studies begin. In this stage, the drug is given to 100 to 500 volunteer patients to determine effectiveness. This phase takes about two years (46).

Only about half the drugs tested in Phase II emerge as successful (46).

If evidence of effectiveness is shown in Phase II, the drug is then given to 1,000 to 5,000 volunteer patients in Phase III, which lasts about three-and-a-half years (46).

Most drugs that are successful in Phase II are also found acceptable in Phase III (46).

After the first three phases of clinical trials are completed, over a total of about seven years, the drug sponsor submits a New Drug Application (NDA) to the FDA. The application includes all animal and human data, analyses of the data, information on how the drug acts in the body, and information on how it is manufactured. The FDA acts on 90% of NDAs within 10 months (46).

"Priority review" of a New Drug Application (NDA) to the FDA is granted to a company seeking approval for a new treatment that addresses an unmet medical need. Under this type of application process, the review period is reduced to 6 months from 10 months. Millennium Pharmaceuticals said their new treatment for bone-marrow cancer was accepted about six weeks after it filed its NDA application with the FDA (182).

After FDA approves a drug and marketing begins, Phase IV studies may commence. These may explore new uses for the drug, new patient populations, and the long-term effects of the drug (46).

On average, only one in five drugs that enter clinical testing is eventually approved by FDA (46).

Each year from 1964 to 1989 pharmaceutical firms filed between 800 and 2,200 investigational new drug notifications with the FDA (19).

Of the 80 to 250 new drug applications (NDAs) companies file annually, each of which can easily reach over 100,000 pages, the FDA approves only 20 to 60 (19).

The number of novel drugs approved by the U.S. Food and Drug Administration peaked in 1996 at 53. There were just 35 in 1999, and 16 through the first half of 2000 (8).

In the U.S. the Food & Drug Administration approved 35 new molecular entities in 1999 (this number does not include product line extension or generic drugs). It was an average year for the industry, which received 30 approvals in 1998 and 39 in 1997 (33).

In the year 2000, only 36% of new-drug applications approved by the FDA were for compounds never sold on the U.S. market. The rest were for reformulations or different dosages, or new manufacturers, of existing drugs (6).

Only 14 new drugs were approved by the FDA in 2002, compared with 32 or more drugs annually in the late '90s (158).

The FDA has lately begun attempts at reformulating itself as a facilitator, in a change from its "gatekeeper" image—often coupled with a notoriously arrogant and defensive attitude (152).

Because the Federal Trade Commission (FTC) has jurisdiction over both product labels and advertising, it shares responsibility for policing drug claims with the FDA (35).

The FTC does not differentiate between health claims and structure/function claims. The scientific standard for advertising claims is flexible, depending greatly on the claim itself—how it is presented and qualified. The bottom line about making claims is that they need to be supported, and companies are responsible for all reasonable interpretations of the claims made in advertisements (35).

The FDA proposed curtailing enforcement of a rule regulating electronic filing of records and data by pharmaceutical manufacturers. The agency said confusion over the scope of the rule, 21 CFR Part 11, and concern about the cost of compliance, is forcing it to review the rule and possibly to revise it. The rule was intended as a means of ensuring the security and integrity of electronic data associated with the manufacture of drugs and active pharmaceutical ingredients (224).

The FDA proposed labeling and manufacturing standards for dietary supplements on March 10, 2003. The rules would establish federal standards to ensure that dietary supplements are not adulterated with contaminants and are labeled to accurately reflect the ingredients (225).

The FDA began reviewing drugs for safety in 1938, and began reviewing for both safety and efficacy in 1962 (226).

On the market since 1964, a New Drug Application (NDA) was submitted for estratest, a hormone-replacement therapy by Solvay SA (Brussels), in 1981. The FDA has yet to rule on its approval (226).

Mark McClellan, the new head of FDA, an economist as well as a medical doctor, said that his goal is to make FDA's drug-review process quicker and more efficient,

thereby reducing the escalating costs of drug development. If successful, his efforts could spur innovation in the pharmaceuticals industry and provide relief to consumers facing high drug bills (357).

Industry and Politics

Pharmaceutical companies shelled out more than \$50M to help Republicans win control of Congress last November (37).

In a coalition against bioterrorism, 32 editors from Nature, Science and other leading journals in the United States and Britain have committed themselves to altering or refusing to publish the tiny fraction of papers submitted to them that could compromise security. At stake: data or results that might help terrorists use toxins or viruses as biological weapons (48).

International Agreements

The World Trade Organization allows countries to bypass patents and manufacture generic versions of patented drugs in case of national health emergencies (78).

The so-called Doha Declaration from the World Trade Organization allows the world's poorest countries to ignore patents when faced with epidemics, including HIV, malaria, and TB (83).

In March 2001, in South Africa, 39 foreign drug companies went to court to challenge a law that would allow the country to buy cheap, generic substitutes for patented AIDS drugs. Meanwhile, Cipla, an Indian manufacturer of generic medicines, asked the South African government for permission to sell inexpensive knockoff versions of 8 of the 15 anti-HIV drugs that, in varying combinations, are used in the cocktails. Cipla said it could offer an AIDS regimen—typically consisting of 3 drugs—for \$600 per patient per year, a small fraction of the \$10,000 to \$15,000 that Americans pay (134).

The Bush Administration blocked a World Trade Organization (WTO) international agreement made in Doha, Qatar, in November 2001 (the "Doha Declaration"), to allow developing countries easier access to generic versions of prescription drugs to combat AIDS, malaria, cholera, and other infectious diseases. The U.S. will allow temporary overriding of American drug-company patents and the export of inexpensive generic versions of brand-name pharmaceuticals to help African and other very poor nations. WTO members agreed to reconvene again in 2003 and try to reach a deal by Feb. 11 (3).

In late November-early December 2002 more than two dozen Republican lawmakers signed letters opposing efforts to dilute the industry's international patent rights in order to make less costly drugs available to patients in poor countries. On Dec. 20, the U.S., alone among the 144-member World Trade Organization, blocked a proposal for distributing patented medicines to less-developed nations. (In November 2001 U.S. Trade Representative Robert Zoellick had signed the Doha

Declaration allowing countries to override drug patents in poor countries to address health crises, such as AIDS and tuberculosis.) (37)

Nutraceuticals and Dietary Supplements

The two pieces of legislation most relevant to the nutraceuticals market are the Dietary Supplement Health & Education Act (DSHEA) of 1994 and the Nutrition Labeling & Education Act (NLEA) of 1990, which established the system for making disease-related claims (35).

NLEA established a mechanism for approving health claims, which link a food or food component to reduced risk of a specific disease. These statements differ from structure/function claims, which state how a substance affects the structure or function of the body. For example, “calcium builds strong bones” is a structure/function claim, but “calcium reduces the risk of osteoporosis” is a health claim. (Currently, only 12 health claims are allowed on product labels.) (35)

The Dietary Supplement and Health Act of 1994 (DSHEA) specifically instructs the Food and Drug Administration to treat dietary supplements as foods (14).

DSHEA allows companies to introduce dietary supplements without FDA approval as long as “there is a history of use or other evidence establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe”. The manufacturer is responsible for ensuring that its supplements are safe, but the burden of proof is on FDA (35).

The Nutraceutical Research & Education Act (NREA) was introduced in Congress by Rep. Frank Pallone (D-NJ) on October 1, 1999. The legislation defines a nutraceutical as a dietary supplement, food, or medical food that “possesses health benefits and is safe for human consumption in such quantity and with such frequency as required to realize such properties”. The legislation is modeled after the Orphan Drug Act (ODA), which encourages pharmaceutical companies to develop drugs to treat rare diseases by making it profitable for them to do so (35).

There are concerns that the nutraceutical market—particularly as regards herbal dietary supplements—is plagued by a lack of science. Efforts are under way to change that (35).

Marketing a nutraceutical product in today's (2003) market is greatly facilitated by serious scientific studies of it by reputable researchers (176)

DSHEA gives FDA the authority to prescribe “good manufacturing practices” (GMP) regulations for the dietary supplement industry (35).

Good Manufacturing Practices (GMP) regulations are about to be applied to the U.S. nutraceuticals market for dietary supplements and ingredients by the FDA in 2003 (14).

The FDA finally moved to impose some quality control on the dietary-supplement industry. The new rules will force supplement makers to deliver the actual ingredients they promise on the label, without contaminants. Under current rules, supplement makers don't have to prove a product is safe or efficacious (183).

The FDA published a 500-page proposal for implementation of good manufacturing practices within the nutraceuticals/dietary supplements industry. The rules are expected to bring uniformity and clarity to the industry, with the intent of ensuring identity, purity, and strength of supplements comprised of everything from vitamins to botanical products (181).

The FDA proposed labeling and manufacturing standards for dietary supplements on March 10, 2003. The rules would establish federal standards to ensure that dietary supplements are not adulterated with contaminants and are labeled to accurately reflect the ingredients (225).

In March 2003, the current level of nutraceuticals sales was estimated at \$13.5 billion per annum (356).

A new bill called the "Dietary Supplement Safety" Act (S.722) was introduced in 2003 in the U.S. Senate. Reaction from the nutraceuticals industry was that the legislation would allow no more consumer protection than current law, embodied in the Dietary Supplement Health and Education Act of 1994 (DSHEA) (358).

Human Microbial Disease

One of the most promising drug-discovery areas involves deciphering the genetic code of microbes and looking at their structure for new ways of attacking them (123).

Common Cold

The common cold occurs at least 500 million times every year in the U.S., and costs \$40 billion, including \$22.5 billion for 20 million lost workdays, plus an estimated 189 million missed school days. The numbers include 110 million trips to doctors, 23.2 million phone calls to physicians and 6 million emergency room visits. More than \$4 billion is spent on self-prescribed over-the-counter medications (which address the symptoms for only a few hours), plus antibiotic prescriptions, most of which are medically useless because the common cold is caused by a virus, not a bacterium. Colds strike every person in the United States on average 2.5 times every year for at least seven days each time (58).

Hundreds of different viruses from several viral families cause colds. Approximately 40% of all colds are caused by rhinoviruses, which attack primarily in the Fall and Spring. Microbes such as syncytial viruses normally attack in the heart of Winter (95).

About 4 million antibiotics prescriptions are written for colds annually, but are ineffective against colds viruses; however, the promiscuous consumption of antibiotics does contribute to the development of antibiotic resistance in bacteria (95).

HIV-AIDS

Number of people living with HIV/AIDS in 1999, 33.6 million (21).

People newly infected with HIV in 1999, 5.6 million (21).

AIDS deaths in 1999, 2.6 million, a higher global total than in any year since the beginning of the epidemic, despite antiretroviral therapy which staved off AIDS and AIDS deaths in richer countries (21).

Total number of AIDS deaths from the beginning of the epidemic to 1999, 16.3 million (12.7 million adults, 6.2 million women, 3.6 million children under the age of 15) (21).

In 2000 there were around 5.3 million new cases of HIV infection, including 600,000 children under 15. Three million were expected to die from AIDS (127).

AIDS has killed about 22 million people since it was first identified more than 20 years ago. Currently (2003), an estimated 42 million people are infected with HIV, with 15,000 new infections each day, most in Asia and Africa (57).

Deaths from those already infected with AIDS will not peak for many years even if prevention programs managed to cut the number of new infections to zero (21).

The prevalence of AIDS continues to grow, and is forecast to grow at least until 2005 (22).

AIDS is ravaging world population growth far more significantly than predicted even as recently as two years ago, in 2001. The U.N. now estimates that by 2050, the population of the nations hit hardest by AIDS will rise by 480 million fewer people because of the impact of AIDS. India alone will account for about 47 million of the increased number of expected AIDS deaths, which China will account for 40 million (173).

The 2002 statistical report from UNAIDS/WHO shows that women, for the first time, accounted for 50% of the adults living with AIDS or HIV. In addition to the 38.6 million adults world-wide with AIDS or HIV, there are 3.2 million children under age 15 who are living with AIDS or HIV. Five million people world-wide became infected in 2002; there were about 3.1 million deaths in 2002. In sub-Saharan Africa, which has been the hardest-hit region, 3.5 million new infections were estimated for 2002; there has been a total of 2.4 million deaths in the region. In Asia, 7.2 million people are living with HIV (64).

Around half of all people who acquire HIV become infected before the age of 25, and typically die before the age of 35 (21).

The overwhelming majority of people with HIV—some 95% of the global total—live in the developing world. This proportion is set to grow even further as infection rates continue to rise in countries where poverty, poor health systems and limited resources for prevention and care fuel the spread of the virus (21).

Sub-Saharan Africa continues to bear the brunt of HIV and AIDS, with close to 70% of the global total of HIV-positive individuals. Most will die in the next 10 years, joining the 13.7 million Africans already claimed by the disease (21).

Most of the 53 nations hit the worst by AIDS are in sub-Saharan Africa, where in 2003 Botswana, Lesotho, Namibia, South Africa, Swaziland, Zambia, and Zimbabwe reported that more than 20% of their populations were infected with HIV. The U.N. projects that, in just a dozen years, the population in these places will be 19% lower than it would have been without AIDS (173).

Life expectancy at birth in southern Africa, which rose from 44 years in the early 1950s to 59 in the early 1990s, is set to drop to just 45 between 2005 and 2010 because of AIDS (21).

Average life expectancy increased to 77.2 years for Americans in 2001, with men living 74.4 years and women 79.8 years (227).

Sub-Saharan Africa continued in 2000 to be the worst-hit AIDS region in the world, with 72% of the new infections and 80% of the deaths in 1999. The region were expected to have 25.3 million people living with HIV/AIDS by the end of the year

2000, 55% of them women. That number corresponds to 8.8% of all adults in the region being infected (127).

In Sub-Saharan Africa in 2000, there were an estimated 3.8 million new cases of AIDS, whereas there were 4 million in 1999 (127).

Estimates for 2002 are that, while 28.5 million Africans are infected with AIDS and 2.2 million died in 2001 from the disease, only 30,000 Africans overall have access to AIDS drugs (up from 2,000 to 3,000 in the year 2000). By contrast, in high-income countries about half a million people are taking AIDS drug “cocktails” and only 25,000 people died of AIDS in 2001 (65).

The AIDS epidemic is exacerbating other crises, notably the famine in southern Africa. Seven million agricultural workers in 25 African countries have died of AIDS since 1985. More than 14 million people are at risk of starvation in Lesotho, Malawi, Mozambique, Swaziland, Zambia, and Zimbabwe. In those six countries, more than 5 million adults and 600,000 children under age 15 are living with HIV, out of a total population of about 26 million (64).

In 1999, Botswana led African nations in the percentage of people, age 15-49, infected with HIV with 36%, followed by Swaziland and Zimbabwe (25% each), Lesotho (24%), and Zambia, South Africa and Namibia (20% each) (128).

The countries with the highest estimated prevalence of HIV/AIDS among adults in 2000 were Botswana (35.8%), Swaziland (25.3%), Zimbabwe (25.1%), Lesotho (23.6%), and Zambia (20.0%) (66).

In the year 2000, AIDS will kill two-thirds of Botswana's 15-year-old sons, and has already reduced life expectancy by more than 20 years (129).

One-third of the working-age adults in Botswana are now infected with AIDS. Life expectancy, now estimated to be in the low 40s, is plummeting and could drop below 30 years by the end of the decade (66).

In Botswana, nearly a third of all adults are infected with the HIV virus. Life expectancy there has already plunged from 65 years in the period from 1990 to 1995, to 56.3 years between 1995 and 2000. In the coming two years, life expectancy there is expected to drop to 39.7 years. Botswana's population is also predicted to decline to 1.4 million by mid-century, down 20% from that in 2000 (173).

South Africa plans to almost double its spending on fighting HIV and AIDS to \$173 million in the next financial year, according to a Government AIDS Action Plan spokesperson (77).

The South African government announced it was investigating the possibility of providing AIDS drugs via the public health system (79).

South Africa has an estimated 4.7 million patients infected with HIV/AIDS, about 11% of the population (79).

AIDS is the top killer of South African women, causing 9.8% of 2001 deaths. Punishment-rapes by AIDS-infected inmates is also a growing prison problem in that country (84).

By 2010, the country of South Africa will be almost one-fifth poorer than it would have been had AIDS never existed (136).

In a Uganda study, transmission rates of HIV between heterosexual couples was found to be generally high (12 transmissions/100 person-years of observation). There were usually no differences in the rate of male-to-female vs. female-to-male transmissions. The HIV RNA level in the donor partner was highly correlated with the risk of heterosexual transmission. No transmissions were documented from individuals with HIV RNA levels < 1,500 copies/mL. For every 10-fold increase in viral load there was a >2-fold risk of transmission (120).

Uganda is perhaps the only African country that has successfully employed behavior modification and an effective approach at bringing down the infection rate of AIDS within its borders, its programs emphasizing abstinence, faithfulness, and condoms, in that order (41).

Many organizations working in Africa regard behavior modification as an unrealistic approach to bringing down the infection rate of AIDS in that part of the world (41).

President Bush last week (2003) proposed a \$15 billion initiative to tackle AIDS in Africa and the Caribbean (41).

UNAIDS estimates that by 2005, \$9.2 billion will be needed annually to provide an expanded response to HIV/AIDS in low and middle-income countries, including \$4.8 billion for prevention and \$4.4 billion for treatment and support. About 10 million of the world's 40 million people infected with the virus, will be sick enough to require treatment in the coming two years (65).

The World Bank pledged virtually unlimited funds to combat AIDS in Africa, where the disease has devastated entire communities (128).

In May 1999, Bristol-Myers announced a five-year charitable donation of \$100 million to help fight AIDS in Botswana and four of its neighbors in southern Africa. Thirteen months later, the program remains mired in a host of unexpected problems (129).

Under a plan developed in 2001, Boehringer-Ingelheim GmbH, a German drug company that makes the AIDS drug Viramune, and Axios International, a Dublin health-consulting firm, have set up an application-and-review process to organize the distribution of the supply of the drug. Boehringer-Ingelheim has offered to donate the drug free of charge for distribution throughout Africa (73).

Merck has cut the price of its efavirenz HIV/AIDS medication for patients in the world's least-developed countries. The new price is 95 cents for a once-a-day 600-

mg tablet, a 30% reduction from the price of the current three-capsule regimen and below the price offered by Indian generic drug companies (68).

Roche Holding AG said that it would sell its AIDS drug, Viracept, an antiretroviral therapy, at about a quarter of its current official price in world's the least developed countries. This brings the treatment in line with the cost of four other major AIDS drugs, whose prices were cut in May 2000. In sub-Saharan Africa and other countries defined as "least developed" by the United Nations, an annual regimen of Viracept will cost about \$900 a patient at current exchange rates, compared with \$3,300 currently. In low-income countries slightly more developed, such as Egypt and Albania, Roche will sell Viracept for \$2,970 for each annual regimen. By comparison, the retail cost in Switzerland is more than \$6,000 a year. Roche also said that additional fees for shipping, taxes, and distribution will be added to the price of the medicines, which could raise the price of the drug by 20% (85).

Several major pharmaceutical companies announced at the 13th International AIDS Conference in Durban, South Africa in July, 2000 that they were developing separate projects to provide poor nations financial and human resources to fight AIDS in African and other parts of the developing world (125).

Profiteers have diverted about \$15 million in cut-price AIDS drugs meant for Africa to the European market, where they were sold for higher prices, according to the Netherlands' General Health Inspection Service. A tiny Dutch company identified as Asklepios imported shipments of two drugs made by Glaxo SmithKline (Combivir and Epivir) to the Netherlands and Germany. Of the 36,000 boxes of drugs intended for Africa, about 30,000 boxes ended up on German pharmacy shelves, while the rest went to the Netherlands. In the Netherlands, a package of 60 Combivir tablets—one month's supply—sells for about EU400 (\$394). By comparison, Glaxo makes Combivir available to certain African countries at discounts of as much as 90% (74).

European Union officials announced a system whereby pharmaceutical companies would have the option of registering and marking with logos cheap drugs destined for the developing world so they could be identified as banned for resale in the EU. Recent media reports revealed that nearly \$18 million of discounted AIDS drugs meant for central African countries had been diverted to markets in Germany, the Netherlands, Switzerland, and the United Kingdom between July 2001 and July 2002 (69).

AIDS activist groups in South Africa are attempting to use civil disobedience to force the government to provide AIDS drugs in public hospitals and clinics (230).

HIV infections in the former Soviet Union have doubled in just two years (21).

HIV cases in the former Soviet bloc rose 60% in 2000 (127).

In 1999, the steepest HIV-rise curve was in the Eastern European/Central Asian regions of the world (21).

In 2000, there were an estimated 250,000 new cases of HIV/AIDS in Eastern Europe and central Asia, bringing the total there to about 700,000 (127).

The AIDS epidemic is spreading fastest in Eastern Europe and Central Asian republics, with 250,000 new infections in those regions in 2002 for a total of 1.2 million people living with HIV or AIDS. In Uzbekistan, for example, there were 620 new infections reported for the first six months of 2002, almost as many as reported for the entire previous decade (64).

In Eastern Europe and the former Soviet Union, the number of people infected with HIV/AIDS nearly doubled from the year 2000 to 2001 (136).

It was estimated that at year-end 2002 there were 4 million HIV/AIDS-infected patients in India (83).

India admits to 4,000,000 infected with HIV/AIDS; the number may be five times as many (136).

The PRC has for the first time permitted a domestic company, Northeast General Pharmaceutical Factory in the northern city of Shenyang, to produce and sell the AIDS drug AZT (76).

China could soon permit generic production of AIDS drugs, according to the Director-General of the Department of Disease Control at the Ministry of Health, if ongoing talks with multinational drug makers to lower the prices of patented drugs that can slow the spread of HIV don't bear fruit (78).

Estimates for 2001 ranged from 800,000 to 1.5 million patients in the People's Republic of China infected with HIV/AIDS. The number of reported cases is rising by more than 30% per year (76).

Chinese health officials estimated that 850,000 people in China (total population about 1.3 billion) had contracted the HIV virus by 2002, an increase of more than 250,000 over 2001. The unofficial estimates for the number of HIV carriers in China have risen steadily from 400,000 in 1999 to 500,000 in 2000 and 600,000 in 2001 (133).

The U.N. says China could have 10 million HIV/AIDS sufferers by 2010 (133).

By year-end 2001, 30,736 people in China had been registered with the HIV virus, among whom 1,594 had full-blown AIDS, and 684 had died. Needle-sharing among intravenous drug users caused 68% of confirmed HIV cases, while illegal blood transfusions accounted for 9.7% and unsafe sex 7.2%. The actual number of HIV/AIDS cases was estimated to be about a factor of ten higher (133).

China is launching a \$4 million program to supply free medicine to thousands of rural villagers with AIDS in Henan Province, in Beijing's first substantial effort to treat AIDS patients amid a growing epidemic. The drugs will be distributed to farming villages in Henan, where unsanitary blood-buying and -donating operations in the mid-1990s spread the disease (163).

In Japan, the HIV prevalent population is expected to grow by 63.9% from 8,980 in 1998 to 14,720 in 2005. This is still a very low overall HIV infected population, however, it may be that the presentation rate for HIV in Japan is very low and the real HIV population is in fact substantially larger (22).

By year-end 2000, an estimated 6.4 million people in Asia and the Pacific will be HIV-positive (127).

The Caribbean has the second-highest rate of AIDS infection after sub-Saharan Africa: more than one in 50 adults is HIV-positive and, because the epidemic is primarily spread heterosexually there, most of the population is at risk (136).

By year-end 2000, an estimated 1.5 million people will be living with HIV in the industrialized countries of North America, Western Europe, and the Pacific (127).

Rates of the spread of AIDS in Western Europe are expected to follow those in the U.S. (22).

The CDC estimated in 1999 that 900,000 persons in the U.S. were infected with HIV (23).

In the year 2000, Canada and the U.S. had an estimated 920,000 people living with HIV/AIDS, including an estimated 45,000 new cases that year (127).

The CDC reported that the decline in AIDS-related mortality in the U.S. is starting to slow and will eventually level off. AIDS deaths dropped for the first time in 1996, decreased by a dramatic 42% in 1997 as many patients switched to new combination drug regimens (often including an HIV protease inhibitor), and dropped by only 20% in 1998 (to 17,047) (23).

The decrease in new AIDS cases showed a slowing pattern—dropping 18% in 1997 but only 11% in 1998 (23).

Sharp declines in AIDS nationally began in 1996 but leveled off in the late 1990s, according to the CDC. In 2001, for the first time in several years, there was a 1% increase in AIDS cases, compared with the previous year. It was estimated that in 2001 there were 41,311 cases of HIV/AIDS-infected patients in the U.S. (87).

Reversing years of sharp declines, diagnoses of the AIDS virus have risen recently in 25 states by 8%, from 15,754 to 16,949, between 1999 and 2001. Among men who have sex with men, HIV diagnoses increased 14% during the same period, from 6,614 to 7,521. Among heterosexuals, HIV diagnoses rose 10%, from 4,973 to 5,468. The survey didn't include some states with high HIV prevalence, such as New York and California, so may not be representative of a nationwide spike (87).

The number of HIV patients in the U.S. is predicted to grow by 24.5% from 689,760 to 858,480 in the period 1998-2005 (22).

The number of new HIV infections in the U.S. is steady at about 40,000 annually, a figure which has not changed since 1990 (23).

The U.S. rate of HIV transmission remains stubbornly high at 40,000 new cases a year and is rising sharply in low-income, minority populations (72).

Levels of both HIV infection and AIDS continue to remain stable in the U.S.; there are approximately 40,000 new infections per annum, and about 4,000 deaths (126).

Recent reports found that a staggering number—as many as 280,000 people in the U.S.—are infected with the AIDS virus and don't know it (87).

The Centers for Disease Control and Prevention (CDC; Atlanta, GA) reported that over half of all new HIV infections in the U.S. are now occurring in people younger than 25 years of age, indicating that HIV infection will not only be prevalent for decades but that newly-infected patients will require treatment for their remaining lives (23).

According to CDC estimates in 2001, about one-third of the 2.1 million people tested for HIV at U.S. public clinics don't come back for their results. Many of these people are poor and transient, making it hard for clinics to track them down (72).

The rate of acquisition of HIV infection among gay men in the U.S. is now four times that of intravenous drug users (23).

The CDC estimates that 8% of U.S. gay males will become infected with HIV in 1999 (23).

For African-American gay men treated at STD clinics, infection rates are as high as 11% a year (126).

AIDS-related mortality is disproportionately affecting minorities. For example, AIDS deaths fell 35% in 1997 and 17% in 1998 for blacks, compared with 51% and 22% for whites (23).

AIDS death rates for blacks remain nearly 10 times higher than for whites and three times higher than for Latinos (23).

Blacks, who compose 13% of the U.S. population, accounted for 49% of AIDS deaths in 1998, while whites accounted for 32% and Latinos for 18% (23).

In 2002, the Centers for Disease Control and Prevention found AIDS-related illnesses remain the leading cause of death for African-American men ages 25 to 44, and the third-leading cause of death for Hispanic men in that age group (64).

AIDS medicines in the U.S. typically cost 5% to 25% more than in most European countries, where drug-price regulations have kept prices lower (62).

In the U.S., state drug-assistance programs pay for roughly 25% of the country's AIDS medicines (62).

In each U.S. state, an AIDS Drug Assistance Program, mainly funded by the federal government, pays for AIDS medications for lower-income or uninsured patients. (The state programs pay for about a quarter of all AIDS drugs, and the federal government's Medicaid plan pays for about a third. The balance is covered privately.) Funding for the program in 2003 was raised by \$80 million, to \$719

million. Program directors claim that still leaves them more than \$100 million short of making ends meet. Fourteen states have capped enrollment in the programs; six other states say they will probably have to take similar measures. In Texas, which runs one of the country's largest AIDS assistance programs, officials say they plan to lower the income level needed to qualify for enrollment, a move that could knock 2,500 people out of the program later in 2003 (62).

State health officials from six states will meet March 17, 2003 with AIDS-drug makers to push the manufacturers for additional rebates for all 56 AIDS drug-assistance programs, or ADAPs, in the U.S. and its territories. ADAPs serve about 80,000 clients, about 30% of the U.S. market for AIDS drugs (175).

HIV infects host cells that express CD4 receptors but also requires chemokine coreceptors (CCRs) for this action. T-lymphocyte-tropic (T-tropic) viruses primarily use the chemokine receptor CXCR4, while macrophage-tropic (M-tropic) viruses use the CCR5 chemokine co-receptor. Blocking the latter prevents host cell infection by HIV-1 (121).

CCR5 receptors are found on the surface of cells, to which the AIDS virus binds, then fuses to the cell (32).

The gp120 protein of HIV binds to cellular receptor sites, while the gp 41 protein binds through the viral membrane (121).

An AIDS research group reported that it has identified an elusive antiviral factor secreted by CD8+ T cells of HIV-resistant people (67).

Scientists have made computer-generated moving images that show how the human immunodeficiency virus that causes AIDS can migrate through a human cell toward the cell's nucleus, where it takes over genetic material to infect more cells. The researchers insert a molecule into HIV that glows green when hit by blue light. Though the virus itself is not visible, the green glow can be seen with a light microscope. The work suggests that HIV is far more infectious than scientists previously believed (52).

A newly-discovered form of HIV, thought to be a sub-type of HIV-1, was first detected in blood samples taken from a 33-year-old female AIDS patient in South Korea who died in 1997; and in a patient in Cyprus who died in 1998 (124).

New studies confirm that people who had HIV and were co-infected with a virus called GBV-C were 2.5 times more likely to survive than those who were not co-infected during an 11-year evaluation period. GBV-C has infected humans for millions of years, but the virus was not actually identified until 1995. The virus is called "C" because it is genetically similar to hepatitis C. The virus does not seem to infect the liver or cause any other adverse symptoms in humans. It is transmitted sexually, through blood products and from mother to infant at birth. Between 1% and 2% of U.S. blood donors are actively infected with GBV-C, and another 13% to 18% have antibodies indicating a previous infection. As many as 40% of HIV-positive individuals have an active infection. The virus binds to the

CCR-5 receptor site on the surface of white blood cells (T-cells) which is the same receptor that is used by HIV. Thus, GBV-C slows HIV viral replication by limiting the number of binding sites available to it (51).

NIH funding for AIDS vaccine research has more than doubled in recent years, from \$130 million in 1997 to \$282 million in 2001. Many scientists believe that the only real chance of stopping the AIDS plague is with a vaccine (135).

The nature of vaccine research is that if the perfect vaccine were discovered tomorrow, it would take almost 10 years to prove it and get it to the regulatory stage (57).

The Aidsvax AIDS vaccine from VaxGen (Brisbane, Calif.) proved a failure in Phase III clinical trials. About 19 other vaccines are currently in human trials (57).

The much-anticipated results of the world's first Phase III clinical trial of VaxGen's AIDS vaccine showed that it was statistically no better than a placebo in preventing HIV infections (188).

Independent scientists were sharply skeptical of a suggestion by VaxGen that its failed experimental AIDS vaccine, Aidsvax, protected some people against HIV infection, arguing that the available data are too weak to support such claims (60).

VaxGen acknowledged that an important piece of statistical evidence buttressing its claims for the efficacy of a controversial AIDS vaccine appears to be weaker than the company had initially asserted. Outside scientists and AIDS activists have criticized the claim of partial efficacy for non-white non-Hispanic subjects, largely because it was based on an analysis of just 29 HIV infections distributed between vaccinated volunteers in that subgroup and those who received a placebo (174).

Many scientists argue that HIV mutates so quickly that vaccines such as Aidsvax from VaxGen, which is based on a chimera of the gp120 protein found on the surface of the AIDS virus, are unlikely ever to work (60).

New findings suggest that the AIDS virus evolves more rapidly than previously thought, underscoring the challenge to develop an effective vaccine. The virus mutates its protective coating at an incredibly rapid rate in order to stay one step ahead of so-called neutralizing antibodies produced by the immune system (229).

Merck and Aventis are combining their two most promising AIDS vaccine candidates in a joint human test in the U.S. that will begin later in 2003 (231).

Three of four monkeys died in a test of a Merck AIDS vaccine that showed early promise, researchers said, casting doubt on the tactic of eliciting a fierce immune response (86).

The number of HIV anti-retroviral drugs under development has fallen by about one-third over the past five years (41).

The advent of more effective combination drug therapy, protease inhibitors, HAART, etc., may be contributing to increased unsafe sex, needle sharing, and

other high risk activities as people erroneously believe that HIV is treatable and no longer a deadly disease (23).

About 30% of patients who begin therapy with a combination of antiviral AIDS drugs have to stop, either because their bodies cannot tolerate the toxic side effects or because they cannot keep up with the grueling regimen of strictly scheduled pill taking. An additional 30% to 50% are currently in salvage therapy, which is what AIDS specialists call the last-ditch potions of drug cocktails given to patients who have become resistant, one by one, to every class of antiviral on the market (106).

The FDA approved an easy-to-use finger-prick blood test that lets patients find out in 20 minutes whether they are HIV-positive (“OraQuick”, OraSure Technologies, Inc., Bethlehem, PA). The test is said to be more than 99% accurate (70).

A researcher reported at a meeting of the Royal Society in London, in September 2000 that mutation rates suggest that a key subtype of HIV-1, which accounts for most AIDS cases in Africa, probably crossed from animals to humans around 1930 (137).

Claims that doctors in Central Africa ignited the AIDS pandemic in the late 1950s by testing polio vaccine contaminated with SIV (the chimpanzee version of HIV) came under heavy criticism from scientists at a meeting of the Royal Society in London, in September 2000 (137).

The U.S. House approved legislation pledging \$15 billion over the next 5 years to fight AIDS overseas, an historic commitment that would be directed at programs for Africa and the Caribbean (359).

Bush’s \$15 billion AIDS package is spurring something of a revolt among disgruntled conservatives concerned about several issues, including the emphasis on condom use (362).

The year 2003 marks the 20th anniversary of the discovery of the human immunodeficiency virus type 1 (HIV-1) (360).

HIV-1 is now the number one killer worldwide (360).

Approximately 70% of the world’s AIDS cases are in sub-Saharan Africa where, in some regions, the seroprevalence of HIV-1 among adults exceeds 25% (360).

There are 42 million people living with HIV/AIDS as of April 2003, 29.4 million of whom are in sub-Saharan Africa (361).

HIV/AIDS looms as a major humanitarian catastrophe for both urban and rural Chinese, and possibly for citizens in the orbit of “Greater China”, such as in Taiwan and Hong Kong (365).

Hemorrhagic Fever Viruses

Ebola is one of the most virulent viral diseases known to humankind, causing death in 50 to 90% of all clinically ill cases. The virus is passed through contact with bodily fluids, such as mucus, saliva, and blood; but is not airborne. The virus

incubates for four to 10 days before flu-like symptoms set in. Eventually, the virus causes severe internal bleeding, vomiting, and diarrhea. There is no cure, but patients treated early for dehydration have a good chance of survival. WHO says more than 800 people have died of the disease since the virus was first identified in 1976 in western Sudan and in a nearby region of Zaire, now Congo (122).

The World Health Organization confirmed that an outbreak of fever during the first week of December 2001 in a settlement about 40 miles southeast of the town of Mekambo in the remote Ogooue Ivindo Province in northeastern Gabon, near the border with the Republic of Congo (which killed 11–10 members of an extended family and a health worker), was an Ebola outbreak. It is the first documented outbreak of Ebola since 2000 in Uganda, where 224 people died from the virus (122).

An Ebola outbreak killed at least 59 of 73 people infected with the hemorrhagic fever in the Republic of Congo, early in 2003. The infected area has been quarantined (157).

The recent Ebola outbreak in the Congo is thought to be linked to the consumption of infected monkey meat (159).

The death toll from the recent outbreak of Ebola in the Republic of Congo has risen to 51, and people have begun fleeing into dense forest to escape what some believe to be an evil spell. Meanwhile, officials have tried to impose tight restrictions on movement in the hope of preventing the spread of the illness, the second outbreak reported in a little over a year in the remote northwest Congo (160).

Ebola is decimating gorilla populations in the Congo Republic according to a primatologist, who said up to 800 have been lost at the Lossi Sanctuary (184).

West Nile virus infected 1,963 people and killed 94 in the U.S. in 2002. The virus belongs to a group including yellow fever virus and St. Louis encephalitis virus, and is transmitted by mosquitoes that pick it up from infected birds. Most people who get the virus show no symptoms. However, about 20% of infected humans develop relatively mild symptoms that can include fever, headache, eye pain, nausea, body aches, rashes, and swollen glands. In some cases it can cause life-threatening encephalitis or meningitis. A handful of patients develop a polio-like paralysis (161).

Herpes Viruses

It was estimated in 1998 that one in five persons over the age of 12 were infected with HSV-2, an increase of 30% since the late 1970s (26).

It was estimated in 1998 that as many as 31 million adults in the U.S. were infected with HSV-2; 500,000 new cases were being diagnosed/treated annually at that time (26).

In 1998 it was estimated that 500,000 to 1 million persons in the U.S. were newly contracting genital herpes each year (26).

By 2002 approximately 45 million Americans were estimated to have genital herpes, but most don't exhibit symptoms (99).

About 25% of persons in the U.S. have detectable HSV-2 antibodies, indicating prior infection (25).

Asymptomatic persons infected with HSV-2 significantly shed virus; many "asymptomatic" infected persons experience but do not recognize or seek treatment for genital herpes recurrences (25).

Once resident in the host body following the initial infection and symptoms, herpes viruses remain dormant in nerve ganglia (the "latent" stage), with irregular herpetic eruptions appearing in response to various stimuli, including psychological stress (117).

Genital herpes can be fatal for infants infected during birth. It is also a risk factor in the spread of HIV/AIDS in adults (99).

The amino acid arginine, which is found in nuts and chocolate, appears to promote the growth of the herpes simplex type 1 virus (100).

The prevalence of genital herpes simplex virus type 2 (HSV-2) infection is greater than 20% among adults in the U.S. Among race and gender, 20% of white women, 15% of white men, 55% of black women, and 35% of black men are seropositive. Eighty percent of HSV-2 infected persons have unrecognized genital herpes, 20% have no symptoms, and 60% have atypical symptoms (369).

HPV

Researchers observed more than 100 years ago that prostitutes had very high rates of cervical cancer, leading to speculation that a sexually transmitted virus caused it. In the mid-1970s, a German researcher isolated HPV in cancerous tissue (82).

There are up to 70-200 strains of HPV. Thirteen have been linked to precancerous or cancerous conditions; four account for 80% of cervical cancer (112).

There are nearly 100 strains of HPV in all, a third of which can be sexually transmitted. HPV-16 and HPV-18 are the strains that are the most common causes of cervical cancer. Two others, HPV-6 and HPV-11, are thought to cause most genital warts (82).

CDC estimates that 75% of the reproductive-age population has been infected with HPV (112).

An estimated 4 million Americans (5% to 20% of persons between the ages of 15 and 49) suffer from genital warts—a sexually transmitted disease caused by the human papilloma virus (HPV)—with 750,000 new cases per year. (Plantar warts, common warts, and genital warts—condylomata acuminata—are all caused by different strains of HPV.) Estimates of genital warts among sexually active adolescent populations are as high as 30%. The prevalence of HPV among sexually active university students is thought to be 46%. Almost half of the women infected with

HPV exhibit no obvious symptoms. The warts may cause itching, burning, pain, and tenderness. Treatment of genital warts traditionally focuses on removal of the warts, which can be painful, e.g., local skin reactions. Pain, burning, and itching are the most commonly reported adverse treatment effects. Currently, no available treatment effectively eliminates genital HPV infection and replication (101).

HPV can be transmitted through non-sexual contact (113).

HPV infection is very common. The virus can be passed by simple touching (82).

It is estimated that there are 5.5 million new cases of HPV in the United States each year, far more than any other STD (112).

Studies have indicated that women have a 20% chance of getting an HPV infection with their first intercourse (82).

One study of female students at Rutgers University in New Jersey found that 26% were already infected with HPV when they arrived as freshmen. The rate was 60% after three years of college (82).

At some point in their lives, up to 80% of sexually active women will have HPV (112).

A study published November 25, 1999 in the New England Journal of Medicine confirmed that persistent human papilloma virus (HPV) infection causes cervical cancer, and that a test for HPV DNA can predict the risk of cervical cancer among women with normal Pap smears (111).

HPV causes at least 90% of all cases of cervical cancer (15,000 cases of which occur annually in the U.S., one-third of which are fatal), which kills more U.S. women each year than does AIDS (112).

Cervical cancer accounts for 6% of all U.S. cancer cases. In 1999, about 12,800 women were diagnosed with cervical cancer, and 4,800 died from it (113).

Estimates are that less than 1% of women who become infected with the two cancer-causing forms of human papilloma virus (HPV) develop cervical cancer or a worrisome condition called "severe dysplasia". Years or decades may pass between infection and disease. Nevertheless, cervical cancer kills almost as many women world-wide as breast cancer. Cervical cancer kills at least 4,000 U.S. women annually and about 230,000 world-wide. More than 80% of the 470,000 annual cases of cervical cancer occur in developing countries. (82).

Males do get HPV and can pass it along, although males exhibit no symptoms at all, not even genital warts (82).

Influenza

Influenza affects 25 million to 50 million persons annually in the U.S., the majority of whom have not received influenza vaccination (20).

The worst flu symptoms, including body aches, chills, fever, and cough, usually occur within the first two to three days, but the illness can linger for as long as two weeks (98).

In the U.S., the flu kills approximately 20,000 people and causes an additional 20-40 million illnesses per year (108).

During an average year, influenza causes 20,000 to 40,000 deaths in the U.S., and results in 300,000 hospitalizations (20).

Each year the flu infects about 1 in 10 adults and kills 20,000 in the U.S. (98).

Flu complications and related pneumonia kill 20,000 to 40,000 Americans every winter, making flu the sixth leading cause of death in the U.S. Flu also causes about 172,000 hospitalizations and \$12 billion in annual costs (110).

Flu killed at least 500 in Congo's north in 2002, apparently spread by refugees fleeing unrest in the Central African Republic. The strain hasn't yet been identified (96).

The recent Congo flu deaths report (see above) was disputed by U.N. officials, who said there had been only 168 flu-related deaths (97).

The annual combined direct and indirect costs in the U.S. of influenza-related healthcare are about \$12 billion (20).

Doctors say the best advice for avoiding flu is to get a flu shot. Ninety million doses should be available in the U.S. in 2002/2003, enough to meet the demand (98).

Flu shots may work as much as 90% of the time in healthy adults, but may be only 30% to 40% as effectively in the elderly (98).

In 1998, only 50% of U.S. flu vaccines protected against the A/Sydney flu virus, which caused 40% of the flu cases that year (95).

During the 1998-1999 influenza season, the CDC recommended that all U.S.-based vaccinations contain the following: an A/Wuhan/359/95(H3N2)-like strain; an A/Bayern/7/95(H1N1)-like strain, and a B/Beijing/184/93-like strain (95).

The 1999-2000 flu season vaccine covered flu types A/Sydney, A/Beijing, and B/Beijing (110).

During the 1999-2000 winter season, the predominant influenza virus circulating was the A/Sydney/5/97(H3N2)-like strain, but the A/Beijing strain was still widely prevalent (95).

Antibiotics are useless against the flu, yet typically about 50% of patients who complain of upper respiratory symptoms are given antibiotics (98).

In 2001, less than 2 million prescriptions were filled for flu drugs, even though about 30 million people suffered from the flu (98).

Taking an anti-flu drug in the first 12 to 48 hours after symptoms appear can shorten the illness by one to three days (98).

Once exposed, family members can take anti-flu drugs for seven to 10 days, lowering their risk of catching the virus by 80% (98).

Monomer helices within the influenza hemagglutinin protein trimer comprise a twisted helix group; helix HA 1 binds to cellular receptor sites (analogous to gp 120 of HIV), while HA 2 binds through the viral membrane (analogous to gp 41) (121).

Norwalk Virus

Holland America Line pulled its cruise ship Amsterdam out of service for 10 days to try to kill the Norwalk gastrointestinal virus—which causes severe diarrhea and nausea—that has contaminated the vessel, afflicting more than 500 passengers in recent weeks. The highly contagious virus has persisted over four consecutive sailings of the Amsterdam despite repeated cleanings by biohazard crews. CDC has registered outbreaks on 11 cruises this year (2002), making this the worst seasonal occurrence of Norwalk in at least six years. The chemical Virkon (a broad-spectrum virucidal disinfectant comprised of a blend of peroxygen compounds, surfactant, organic acids, and an inorganic buffer system) kills the virus (105).

Los Angeles County has seen a spike in outbreaks of norovirus, the category of viruses that sickened thousands of cruise passengers last year. There have been 23 outbreaks of Norwalk-like virus in the last six months, compared to just three during the same period last year. The family of viruses causes short-lived, gastrointestinal illness. Symptoms such as nausea, vomiting, diarrhea and stomach cramps typically last one or two days and don't require medical attention. The highly contagious viruses can be transmitted person-to-person through the air, food and water. Between Sept. 1, 2002 and Feb. 21, 2003, the outbreaks sickened at least 407 people. The Centers for Disease Control and Prevention estimates there are 23 million cases of Norwalk-like virus infection each year (49).

SARS

Experts have ruled out avian flu (A[H5N1]) as the cause of SARS (193).

CDC has tentatively identified the SARS virus as a type of paramyxovirus, a large virus family whose members cause such human diseases as mumps, measles, and parainfluenza, as well as an array of animal diseases. One newly discovered paramyxovirus, Nipah (named after the Malaysian village where it was identified), which was discovered in 1998, killed 105 Malaysian pig farmers (203).

A leading suspected cause of SARS is a pig virus—Nipah—a member of the paramyxovirus family (198).

While the cause of SARS has not yet been pinpointed, there are some indications of Nipah virus, a newly identified pig virus responsible for sickening and killing swine farmers in the late 1990s (199).

The closely-related Hendra and Nipah viruses were being examined as possible causes of SARS(201).

German officials tentatively identified the cause of SARS as a paramyxovirus, although some symptoms were not an exact match (205).

SARS now thought to be a coronavirus, which is linked to respiratory disease in chickens and pigs (207).

CDC said its leading suspect for SARS is a new member of the coronavirus family, known until now for causing common colds in humans (209).

Coronaviruses were first isolated from chickens in 1937. By the late 1960s, researchers had concluded that they are responsible for about half of all common colds. The viruses can also cause health problems in cattle, pigs, rodents, cats, dogs, and birds. There is no specific treatment for the viruses, which take their name from the crown-like protrusions on their surfaces. Coronaviruses are normally quite infectious (208).

CDC reported that SARS appears to be the result of a new or emerging coronavirus (212).

Scientists say a new version of a coronavirus is to blame for SARS (215).

University of Hong Kong researchers identified a coronavirus as the cause of SARS (219).

Most scientists are now convinced that a new coronavirus causes SARS, and some want to rename the disease coronavirus pneumonia (CVP) (221).

On April 7, the WHO stated: "It is currently agreed that [a novel] coronavirus (SARS virus) is the major causative agent of SARS. Human metapneumovirus (hMPV) has also been found in respiratory specimens and antibodies against hMPV in serum of some SARS patients, as well as evidence of dual infection with hMPV and the SARS virus. The significance of hMPV in SARS remains unclear at this time and will be reported on later" (237).

The SARS virus may have originated from farms in China, where pigs and ducks are raised together in close proximity. Ducks are the reservoir of influenza diversity, and pigs are a mixing vessel for mammalian influenza strains (263).

Just two months after SARS was recognized worldwide, scientist not only identified the culprit but fully decoded its genetic makeup (238).

The genome of the SARS virus was first decoded by a team of Canadian researchers at the Genome Sciences Center of the British Columbia Cancer Agency and

distributed to scientists on the Internet in April. The work is part of a steady acceleration of efforts to understand the biology of the SARS virus, and to develop effective treatments to stop it (241).

CDC finished genetic sequencing of the SARS virus, finding near-identity with the results of the Canadian effort (246).

Dr. Gerberding, head of CDC, commented that the SARS genetic sequence “is not a magic bullet for dealing with SARS” (246).

AIDS researcher David Ho said he has agreed to conduct work on potential therapy and vaccine approaches for SARS. He stressed that most of those strategies would take years to bear fruit (245).

CDC warned that a vaccine to protect against SARS remains at least a year away (246).

Elegantly simple, viruses replicate themselves by sabotaging a host cell’s production machinery, forcing it to make countless copies of the virus. For example, the coronavirus enters a host cell by fusing with the cell membrane; it then releases its viral RNA into the cell. Once the RNA is inside the cell, it is translated into proteins which are then assembled into virus particles. As the particles migrate toward the cell membrane, they aggregate to form new coronaviruses, which then leave the cell to infect other cells (240).

Robert Webster, a flu virologist of St. Jude Children’s Hospital in Memphis, Tennessee, said he believes there are multiple strains of the SARS virus, the Canadian strain being substantially more virulent than the U.S. strain. Julie Gerberding, director of CDC, said too few samples had been tested to draw any conclusions (242).

Researchers in Hong Kong said the SARS virus is mutating rapidly into at least two forms, complicating efforts to develop a solid diagnosis and a vaccine. WHO scientists say the coronavirus family is prone to mutations (243).

Scientists in the U.S. and Hong Kong have developed tests to detect SARS, an important step in helping public-health officials track the disease. The diagnostic tests confirm the presence of the virus by measuring the antibodies a patient builds to fight the illness. The tests can separate those patients with SARS from those who have the flu or another respiratory disease (251).

Diagnostic companies are moving quickly to create and distribute improved tests to help determine whether a patient has SARS. A German biotech firm, Artus GmbH, is the first company to begin distributing a test that can identify the presence of the virus in sputum or a stool sample. The company said it has sent out 6,000 test kits at no charge to researchers in Singapore, Hong Kong, and elsewhere in Asia (252).

Thermal imaging is being used to screen people for SARS at Singapore customs checkpoints (253).

Infectious-disease experts are pushing a plan to study and treat SARS patients at the National Institutes of Health's Clinical Center, prompting protests from some NIH cancer specialists who say the move could imperil patients with impaired immune systems as well as workers at the facility (254).

The incubation time for the SARS virus is thought to be about 10 days (243).

SARS may be less aggressive in children, compared with teenagers and adults (260).

SARS symptoms include sudden onset high fever, muscle aches, headache, sore throat, dry cough, shortness of breath, and low WBC and platelet counts. X-rays show signs of pneumonia or respiratory distress syndrome, often in both lungs (193).

People infected with the SARS virus may experience the following symptoms: high fever (greater than 100°F), dry cough, shortness of breath or breathing difficulties, changes in chest X-rays indicative of pneumonia; and/or headache, muscular stiffness, loss of appetite, malaise, confusions, rash, or diarrhea (247).

Frank Plummer of Canada's National Microbiology Laboratory in Winnipeg, Manitoba, said he found the SARS-linked coronavirus in healthy and mildly ill people who were exposed to severe acute respiratory syndrome and also in some who weren't believed to have been exposed to the virus. The results may mean that there is a broader spectrum of illness that is not captured among probable and suspect cases. It isn't clear whether people with mild or no symptoms can infect others (244).

As with most respiratory viruses, it is probably fair to assume that individuals may be infectious during the incubation period of 2-10 days. Once a patient is symptomatic, transmission to others is known to occur (259).

Two disease specialists are debating the theory of whether some people with SARS might be "superinfectors" or "superspreaders"—that is, unusually contagious and able to transmit the illness to larger numbers of people. In China's Guangdong Province, one man spread the disease to more than 30 people. Only one of the 30 people he infected went on to transmit SARS, and that person infected just two others. In Singapore, a woman sickened 50 family members, friends, and contacts, along with 56 health-care workers. In Toronto, a man infected as many as 30 others (256).

SARS-affected countries have adopted widely divergent postures toward the disease, ranging from denial to reasoned caution to mass quarantine of even the healthy (255).

SARS may exhibit a seasonal infection pattern, somewhat similar to influenza outbreaks, which are usually limited to the late fall and winter (257).

Some of the cities most affected by SARS are experiencing rising spring temperatures, which usually bring a big drop in respiratory infections. Experts, however, say it's too soon to tell if SARS infection rates will change with the seasons. They nonetheless worry that the recent drop-off in new cases could be just a lull, since the SARS virus, like the flu, could re-emerge again next winter (258).

As cases of SARS mushroom across China, the epidemic appears to be coming under control in several ther affected areas, thanks mainly to aggressive isolation efforts. The WHO declared Vietnam the first country to have successfully contained SARS, after it went 3 weeks without reporting new cases. Singapore has reported no additional cases for 2 days in a row. New infections in Canada, the only country outside Asia to have experienced SARS deaths, have dropped off similarly. In Hong Kong, 14 new cases were announced, the lowest daily number since March 16 (264).

Governments find that isolation of suspected SARS cases is difficult to effect and enforce, e.g., in Hong Kong (285).

Sorting the facts, guesses and mysteries of SARS: the culprit virus has been found, but how it spreads is murky; whether there will be a SARS season has yet to be determined (262).

The close proximity of ducks, chickens, pigs and humans in China can create a toxic stew. Ducks are incubators of viral diseases such as influenza and SARS, pigs act as hosts, and the virus then jumps to humans (286).

Hong Kong scientists are concerned that the virus may survive in an infected person's body for at least a month after recovery (243).

Scientists in Hong Kong said they feared that 12 recovered, symptom-free patients may have relapsed (243).

As many as a thousand drugs already licensed for other viruses are being screened at Ft. Detrick, Maryland, to see if any might combat coronaviruses (249).

Marc Collett, ViroPharma's vice president of discovery research, warned that designing a new custom-made drug for SARS or any emerging virus is a five year program (249).

SARS apparently first appeared in Foshan, China, a city near Guangzhou, in mid-November 2002. China did not seek WHO help until March 2003 (200).

Health officials have traced the spread of SARS to a semiretired medical professor and kidney specialist, Liu Jianlun, from the Chinese Province of Guangdong, who caught the illness at the Guangdong Hospital known as Sun Yat-Sen Memorial No. 2, where he worked before traveling to Hong Kong in mid-February, when he unwittingly transmitted it to at least seven people staying or visiting on the same floor of a hotel. These people then carried the disease worldwide. The first case is believed to have been a seafood merchant from the city of Guangzhou, the capital of Guangdong (202).

Finding the origins of SARS is seen as a long and difficult task (239).

SARS spread worldwide beginning with infected passengers on a flight to Beijing from Hong Kong (218).

China revealed that a lethal virus, SARS, has caused an additional 12 deaths and hundreds of new cases, and said it would allow a team of foreign specialists to visit the area where the outbreaks first occurred (287).

As new theories emerge about how the deadly form of SARS is incubated and spreads, a prominent Beijing surgeon alleged that China is still playing down the impact of the disease (288).

SARS appears to have an incubation period of as many as 16 days, significantly longer than the 10- to 12-day surveillance period the WHO and CDC recommend health authorities use (288).

WHO wants to investigate the Chinese handling of SARS, following Chinese officials' failure to explain reports that the outbreak is more widespread than the government says (289).

WHO officials, in their third week of a SARS inspection tour, said bluntly at a news conference in Beijing that they haven't received sufficient information to determine the scale of the outbreak in China, and disbelieve figures supplied by the Chinese government (290).

Beijing authorities are only slowly granting access to a WHO team investigating SARS, raising concerns about whether further outbreaks of the flu-like illness can be controlled world-wide without the full cooperation of China (291).

China's government publicly acknowledged that the spread of SARS poses serious risks for the country. After weeks of assuring the public it was under control, Premier Wen Jiabao called the containment of SARS not only a matter of public health but of economic stability (292).

China's capital Beijing is drawing a lesson from Hong Kong and Singapore in quarantining more people at risk for SARS. Beijing's new aggressiveness in fighting SARS is also raising questions about its previous efforts, particularly concealment of the extent of the outbreak throughout China (293).

Hong Kong's densely packed high-rise housing blocks may be a key reason that SARS is spreading faster here than in other urban areas affected by the disease (294).

The SARS toll continued to grow in Hong Kong, which posted its largest one-day death toll of 12 on April 19, and another 7 deaths April 20 (295).

Hong Kong reported April 19 a record 12 deaths in a single day from SARS, and Singapore's leader warned the SARS outbreak could be the worst crisis the country has ever faced (298).

SARS problem grows for Chinese officials in remote provinces, already slow to respond, underscoring challenges Chinese authorities face as the virus spreads into the country's vast hinterland (296).

China's leaders, confronted with growing anger at home and abroad over their slow response to the SARS outbreak, fired the country's health minister as well as the mayor of Beijing, admitting publicly that the number of SARS patients in the nation's capital is almost 10 times the number previously reported (297).

China, under fire at home and abroad for failing to disclose the extent of its SARS infections, sharply raised its number of cases on April 20 to 1,807 from 1,512 and revealed scores of new infections in Beijing (299).

Local MD, Dr. Jiang Yanyong, went public decrying Beijing's concealing the true magnitude of the SARS crisis in China (300).

China's belated candor about the spread of SARS has resulted in near panic. The Shenzhen and Shanghai stock markets both fell on SARS fears (301).

China's health minister and mayor of Beijing were both fired, confirming that a major debate has been taking place behind the Communist Party scenes over the handling of the SARS crisis (302).

The SARS crisis is threatening China's social and economic stability, as well as fostering popular discontent with its political system (303).

China's capital faces a crucial week—May 8—that could determine the outcome of the nation's battle to contain SARS, a challenge it approaches with its medical system already vastly strained (304).

SARS has landed China's rulers with what may be the biggest challenge to their power in the country's 25-year reform era. The political fallout is the result of a long-brewing clash between an increasingly assertive population and an antiquated political system (305).

As SARS began infecting hundreds of patients some six weeks ago, Hong Kong's medical community improvised a treatment combining the antiviral drug ribavirin with corticosteroids, which act as an anti-inflammatory. Recent spikes in SARS deaths, however, are raising doubts about the efficacy of the treatment (306).

The SARS tally in China is surging, just as the country prepares for a holiday that typically puts the whole nation in motion, now at the risk of spreading the disease to smaller cities and towns unable to cope with a health crisis (307).

Across China, many citizens kicked off what was to be their weeklong spring vacation yesterday by staying at home. This year the Chinese government is appealing to its citizens in the name of national health and security to cancel vacations in order to help stem the outbreak of SARS, which by now has extended into 26 of China's 31 provinces (323).

The city of Beijing on Thursday attempted lockdown measures to contain the spread of SARS, which served only to illustrate official impotence in the face of a population that is freer than ever before from official constraints. Rumors sweeping Beijing that declaration of martial law was imminent have fed a panicked exodus that has been building for days (308).

Beijing imposes new SARS curbs as the city's theaters and cafés are shut down (309).

As the number of SARS cases have continued to mount, confusion is starting to take a toll on adoptions from China (310).

Fears over the spread of SARS in Hong Kong have prompted a backlash against cats, dogs, and other household pets (311).

Retail sales in Hong Kong posted their biggest decline in nearly four years in February, while an industry group and analysts warned the slump likely worsened in March as the SARS outbreak sapped domestic demand (312).

The SARS virus is creating economic ripples in China. The tourism industry is taking a big hit in the form of canceled hotel and flight bookings; consumer demand could weaken further. Investor nervousness also looms (313).

The SARS outbreak has meant new business for at least two industries: China's private-jet firms catering to executives and others seeking to escape the problem; and telecommunications services for stay-at-home workers (314).

SARS scare batters Hong Kong's Cathay Pacific Airways. SARS worries and low passenger traffic have forced Cathay Pacific to cut back service to many major destinations (315).

Toys are an industry—\$11 billion worldwide—that could be hurt if Chinese factory workers fall ill with SARS (316).

As SARS spooks passengers from traveling in many parts of Asia, the cruise industry is scrambling to keep the virus off its ships in Asia and around the globe. The industry is already suffering from a prolonged slump in bookings and prices, and the last thing it needs is the appearance of an illness more feared than the Norwalk stomach virus, an ailment that hit various cruise lines last Fall (317).

Economists now say China's economy will take a hit from SARS, with growth possibly slumping below 7% to its lowest level in nearly a decade (318).

The spread of SARS in China has delayed the long-awaited opening of A shares to foreign investors on the Shanghai Stock Exchange (319).

With regulators in China turning their attention to efforts to reduce the spread of SARS, the opening of China's A-share market to foreign investors appears to be delayed (320).

An important gauge of economic activity in Hong Kong, the purchasing manager's index, showed its lowest reading ever last month, underscoring the effect of SARS on the city (321).

The SARS crisis hasn't necessarily robbed China of its long-term luster in the eyes of many U.S. manufacturers looking to invest in new factories there (322).

WHO has issued a global pneumonia alert after a highly contagious respiratory illness killed one man and infected nearly 60 hospital staff in Hong Kong and Vietnam. There was an outbreak of atypical pneumonia in China's southern Guangdong Province in mid-February which infected 305 people, killing five. It is not known if the Guangdong cases are linked to the ones in Hanoi or Hong Kong (196).

The World Health Organization (WHO) has declared Severe Acute Respiratory Syndrome (SARS) to be a worldwide health threat. Over 300 people have been affected by it in Southeast Asia since November 2002; 10 other cases, including 2 patients who died, are suspected in Canada, and at least one person with SARS has traveled to New York City (193).

Toronto's SARS outbreak is at a critical juncture, as thousands of staff and visitors who were at risk of exposure at the city's Scarborough Grace Hospital began a 10-day quarantine period a week ago (324).

Canada has more than 300 possible cases of SARS, with 14 deaths, as of April 22. Teams of health workers meanwhile race to contact thousand who may have crossed paths with the virus (325).

Toronto health officials sounded optimistic about the city's outbreak of SARS, noting that the number of cases showed a decline recently (326).

As of April 7, Toronto had 188 cases of SARS. Ten died, and an 11th death is under investigation (328).

Toronto is battling the biggest SARS outbreak outside of Asia. Doctors are now taking precautions to contain the virus, but at first worked at a disadvantage because SARS hit Canada about a week before WHO issued its global warning on March 12 about the disease spreading from Asia. As a result, the disease spread unchecked in Toronto for days, aggravated by interhospital transfers of patients who hadn't yet been diagnosed (328).

The WHO is advising against travel to Toronto in light of the SARS outbreak there, a move that provoked angry responses from local Canadian officials and handwringing in the travel industry (329).

WHO said it will review its advisory recommending against nonessential travel to Toronto, following a torrent of criticism and lobbying from Canadian public health officials and politicians (330).

With the outbreak of SARS in Toronto waning but tourism still suffering, public-health officials are changing their message to emphasize the declining number of current cases and the low risk of SARS to the general public (331).

On April 29, WHO reviewed its recommendation against nonessential travel to Toronto (331).

On April 30, WHO lifted its advisory against nonessential travel to Toronto, after Canadian health officials convinced it that the city's outbreak of SARS is under control and not spreading in the community (332).

As of April 19 the number of Canadian deaths from SARS had risen to 6, while a Toronto doctor leading the fight against the disease, Dr. Donald Low, chief microbiologist at Toronto's Mount Sinai Hospital, went into quarantine (333).

As of May 2, outside of mainland China, Taiwan's SARS outbreak was the fastest moving in all of Asia (335).

The CDC issued a travel advisory warning Americans not to travel to Taiwan. Taiwan has postponed indefinitely Asia's biggest computer trade show, Computex Taipei, and has begun quarantining visitors from other affected areas (335).

After weeks of keeping the island relatively free of SARS, Taiwan health officials are struggling to contain eruptions of the virus at two hospitals, both of which have been put under quarantine (334).

The recent hospital lockdown in Taiwan appeared to have backfired, as the virus continued to spread (335).

As of May 2, the total number of SARS cases in Taiwan had risen from none on March 16 to 85 (336).

SARS is quickly spreading around the world. Reports of cases have come in from Canada, China, Hong Kong, Taiwan, Indonesia, the Philippines, Singapore, Thailand, and Viet Nam, prompting the WHO to issue a global alert for the first time in more than a decade (195).

Stay put, wear a surgical mask, and teleconference are some of the panic-tinged bits of advise that multinational companies are giving to employees who either work in or frequently travel to Hong Kong and other parts of Asia, which is gripped by a mysterious viral pneumonia epidemic (265).

SARS has set off alarm bells among world health authorities, who have reacted quickly to contain its spread. However, the intensity of the response, as well as the death of a doctor who was among the first to identify the disease, is unnerving and confusing to many (266).

Airlines are facing tighter scrutiny from governments, passengers and even their own flight crews because of the spread of SARS (267).

Despite efforts by health officials in the U.S. and overseas to allay public concerns, jitters about a new and highly contagious form of pneumonia appear to be spreading as rapidly as the illness itself (268).

The number of cases of SARS is likely to fluctuate until health officials around the world get a better handle on the disease. WHO reported 167 cases and four deaths to date, but those figures don't include hundreds of illnesses and five reported deaths from what could be a related outbreak in China. Officials believe the disease is spread person to person by respiratory or nasal droplets, but only through close contact, such as that among household members or health-care workers (197).

During the past week or so, about 150 people in 10 countries or territories have been diagnosed with SARS. At least nine people have died, including an American businessman who fell ill in Hanoi, a nurse in Vietnam who treated him, and a woman and her son who died in Canada after returning from Hong Kong (198).

WHO was investigating apparent SARS cases in Britain, France, Israel, Slovenia, and Australia. There were reports of two SARS deaths in Canada and a suspected case in Germany (201).

The number of SARS cases has grown to 39 suspected cases in 18 U.S. states, 419 worldwide. So far, 17 people in Hong Kong, Vietnam, and Canada have died of the disease. (The totals do not include 300 more suspected cases and five deaths reported earlier in China.) (208).

The number of SARS cases has grown to 37 in the U.S., and 401 worldwide in 15 countries with 11 deaths. Sixteen of the cases are in Europe—seven in Switzerland, two each in Germany, Italy, and the U.K., and one each in Ireland, Slovenia, and Spain (207).

Public-health officials told U.S. lawmakers on April 7 that it was too soon to tell whether a sometimes deadly respiratory illness infecting people around the world would present a permanent health threat or if it would recede or be contained (337).

With SARS now spreading farther and faster than health officials expected, U.S. hospitals are calling on some of their new bioterrorism skills and resources to contain the disease. As of April 1, 69 cases of SARS in the U.S. had been reported (338).

Voluntary isolation and quarantine are working well to contain the small number of SARS cases in the U.S. But if the outbreak mushrooms as it has in Asia, officials worry that more sweeping measures could strain the system and erode public compliance (339).

Recent upgrades to the public health system have improved the U.S.'s ability to respond to a large-scale outbreak of SARS, federal health officials said (340).

On April 17, CDC tightened its definition of SARS, with only 35 people in the U.S. qualifying as having "probable" cases of the disease (341).

A blend of luck, mild cases, solid public health, and advanced warning has thus far spared the U.S. from a more violent outbreak of SARS (342).

A 47-year-old Florida woman with a suspected case of SARS apparently got the virus from a co-worker. It would mark the first time SARS has spread in the U.S. beyond medical workers and people living with those who are already sick (343).

As of April 1, there were 14 SARS cases in California, 10 in New York, and about 40 more spread throughout the U.S. (344).

As of April 9, CDC had received 166 reports from 30 states of suspected SARS cases among U.S. residents; 135 (81%) cases occurred among adults (345).

During November 1, 2002–April 17, 2003, a total of 208 SARS cases were reported to CDC from 34 states (346).

During November 1, 2002–April 16, 2003, a total of 3,293 SARS cases were reported to WHO from 22 countries; 159 deaths (4.8%) were reported (346).

As of April 9, a total of 2,722 SARS cases had been reported to WHO from 16 countries, together with reports of 106 deaths (3.9% case-fatality proportion) (345).

As of Monday, March 24, 2003, the number of suspected SARS cases reported by WHO has increased to 456, up from 350 the previous Friday. Seven new deaths have been reported (211).

Between February and March 26, 2003, SARS had sickened 487 people and killed 17 (219).

Since November 2002, there have been more than 1,400 reported cases of SARS in 14 countries; more than 50 people have died, including 34 in China, 11 in Hong Kong, and a handful each in Singapore, Vietnam, and Canada. So far, 51 cases have been reported in the U.S., but no deaths. All but seven of the U.S. patients are believed to have caught the disease while traveling to Asia (220).

As of April 16, the SARS virus totals 3,235 cases in 23 countries, with a suspected 154 deaths (238).

While health officials in Hong Kong and China scrambled to cope with a raft of new cases of SARS, concerns over the disease ebbed in Vietnam in early April, where no new cases had reported for the previous 9 days (347).

More cases of SARS were identified in Hong Kong, where the infection had spread to several hospitals and a private clinic, infecting nearly 50 people, mainly medical staff. Two are in serious condition (194).

U.S. businessman contracted SARS in Hanoi, died in Hong Kong hospital March 13 (206).

The region most severely affected by SARS is Hong Kong, which as of March 24, 2003 had reported 260 cases and 10 deaths (208).

Some Hong Kong hotels have reported as many as 80% of bookings postponed because of SARS. Tourism in Southeast Asia in general has been severely affected because of the outbreak (210).

Dr. William Ho, chief executive of the Hong Kong Hospital Authority has contracted SARS (213).

Hong Kong was considering a Singapore-style massive quarantine in an attempt to halt the spread of SARS. Singapore has already ordered a 10-day quarantine of 861 people, and closed all schools (216).

SARS spread from hospitals to the general populace in Hong Kong. The Rolling Stones band cancelled its Hong Kong concerts, scheduled for March (217).

Hong Kong officials reported another 105 cases of SARS over the weekend. CDC issued a travel warning, which advised Americans to postpone trips until further notice to mainland China, Hong Kong, Singapore, and Hanoi (222).

China delayed 4 months in informing WHO of the SARS problem (204).

Some blame China's policy of secrecy surrounding SARS for its spread to the rest of the world (223).

China updated its reported statistics on SARS cases; nearly 800 are said to have been infected, with 34 dead. The figures bring the global number of cases to 1,323—including 45 in the U.S.—and 52 deaths. Worst-hit outside Mainland China is Hong Kong, with about 300 SARS cases and 11 deaths (214).

China issued a rare apology for a lack of publicity on the initial outbreak that it acknowledged would have helped in understanding the disease (239).

The Canadian government said it would set aside US \$70 million in 2003 to protect Canadians and visitors from SARS. Canada has had 349 probable or suspected cases, with 23 deaths (243).

In Malaysia, 60 more patients and staff were quarantined at two hospitals feared to be sites of a SARS outbreak (243).

Singapore reported two new SARS cases and another death on May 2, bringing total deaths to 25, the world's third-highest number (243).

The SARS death rate remains at about 3.7% (209).

WHO officials said in May that the SARS fatality rate was worsening as patients who had been lingering in hospitals had begun to die from the disease (243).

WHO said that the death rate from SARS may have risen to 10 percent from 6 percent, especially in Canada and Singapore (243).

Analysis of the latest statistics on the global SARS epidemic reveals that at least 10 percent of people who contract the new virus will die of the disease (248).

The WHO maintains that the mortality rate for SARS is currently about 5.6%. But some medical officials believe the real mortality rate may be 10.4%, because in its

calculation the WHO includes not just known cases of recovery from the disease but also patients who remain hospitalized—in other words, people who may yet die (261).

New SARS figures were released from Beijing on April 3. There have been 1,190 cases to date, with 46 deaths. Separately, sixteen deaths from 708 cases were reported from Hong Kong (269).

Health team visits southern China in an effort to visit the first site of the SARS outbreak (271).

As of April 7, countries with the most reported cases of SARS were: China (1220; 52 deaths), Hong Kong (800; 22 deaths), Singapore (106; 6 deaths), U.S. (115; 0 deaths), Canada (217; 9 deaths), and Vietnam (59; 4 deaths) (272).

As of April 10, the SARS totals were: world, 2,986 cases (up from 1,485 on March 28, 167 on March 17); China, 1,290 cases (up from 806 on March 28); and Hong Kong, 998 cases (up from 425 on March 28 and 95 on March 17) (273).

Insurance companies are now excluding coverage for SARS from policies written to insure conventions, sporting events and trade shows world-wide. Insurance companies began applying the exclusions two weeks ago, and the exclusions are now universal (274).

Forecast losses in economic output in 2003 due to SARS: China, \$2.2B; South Korea, \$2.0B; Hong Kong, \$1.7B; Japan, \$1.1B (275).

SARS has dealt a severe blow to Asian economies. Analysis shows the virus could drain \$10.6B from 2003's forecast GDP (277).

The outbreak of SARS is beginning to affect U.S. businesses in many ways. For example, many multinational companies have put up a fire wall between their headquarters and Asian operations (278).

As of April 22, there were 3,861 probable cases of SARS world-wide. An additional 217 people had died of the virus, and 1,873 had recovered (276).

Confirmed SARS cases world-wide as of April 25: China, 2,422 (110 deaths); Hong Kong, 1,483 (109 deaths); Singapore, 192 (19 deaths); Canada, 140 (16 deaths) (279).

SARS adds red tape to travel; air passengers face SARS-related delays in various Asian countries and Canada in efforts at controlling the spread of the virus (280).

SARS represents the biggest economic challenge to Asia's governments since the financial crisis of 1997-1998. Many consumers are wary of going out shopping, dining, or traveling (281).

As of May 1, deaths attributed to SARS were: China, 170; Hong Kong, 162; Singapore, 25; Canada, 23 (282).

Inside the WHO as it mobilized for SARS: U.N. Agency's envoys argued in Hanoi, cajoled in Beijing, in efforts at alerting the world (283).

An increasingly global work force helps spread diseases such as SARS, which circled the globe via Toronto (284).

Smallpox

A polyethylene glycol-treated ("pegylated") version of cidofovir, a Gilead Sciences, Inc. (Foster City, CA) antiviral compound used to treat an AIDS-related eye infection, when taken before or after exposure to a lethal cowpox virus (a smallpox-like virus) infection reduced death rates in mice (185).

Analogues of the antiviral agent cidofovir show efficacy in both the prevention of orthopoxvirus infection and as a post-exposure treatment (228).

Blood-Related Disease

Bayer AG and Aventis SA called off a deal to pool their plasma-products businesses, dashing plans to create the world's largest maker of blood-related drugs (45).

Only a handful of companies operate in the global plasma market. The largest is Baxter International, which supplies about 25% of the world's blood-plasma-related products (45).

In 1995 the estimated risk of transmitting HIV by the transfusion of screened blood was thought to be very small—per 12 million screened blood donations 18 to 27 were believed to be infectious (28,29).

West Nile Virus

In late summer and early fall of 1999, human West Nile virus (WNV) infections were recognized for the first time in the Western Hemisphere (369).

Since its original introduction into the New York City area, WNV has caused disease in humans, horses, and a wide variety of birds and other vertebrates (369).

WNV has spread into the eastern two-thirds of the U.S. and also into Canada and the Caribbean Basin (369).

The apparent ability of WNV to be disseminated by infected birds and to persist from year to year indicates that it will continue to be a public health problem for the foreseeable future (369).

Twenty-nine laboratory-confirmed West Nile virus (WNV) encephalitis patients were bled serially so that WNV-reactive immunoglobulin (Ig) M activity could be

determined. Of those patients bled, 7 (60%) of 12 had anti-WNV IgM at approximately 500 days after onset (369).

Veterinary Microbial Disease

Cattle

Once a net importer of beef, Brazil is now the third-largest exporter in the world, behind the U.S. and Australia. In the past three years alone, Brazil's exports tripled to 750 thousand tons, as it won new markets in Europe, Asia, and the Middle East. Brazil is home to 165 million head of cattle, and now boasts the largest commercial herd in the world (115).

Talks between Brazil and the U.S. regarding the importation of beef from the former country were suspended last year after a bout of foot-and-mouth disease in the southern state of Rio Grande do Sul. Police troops slaughtered thousands of cattle infected with the viral disease, which prevents cows from eating and often causes their death (115).

Chickens

The California Department of Food and Agriculture and the U.S. Department of Agriculture received laboratory confirmation in December 2002 of exotic Newcastle disease in commercial egg-laying facilities in California. As of December 30, the regional quarantine zone in California included the counties of Los Angeles, San Bernardino, Orange, Riverside, and San Diego (146).

The federal government and Gov. Gray Davis both declared a state of emergency in Southern California because of an outbreak of exotic Newcastle disease, which threatens the state's \$3-billion poultry business. About 650 people have been assigned from different agencies to work on eradicating the disease. State officials have called for the destruction so far of about 1.2 million chickens to contain the outbreak, which was first discovered in backyard chicken flocks in Compton in September, 2002. The quarantine area for the disease was expanded to include Santa Barbara, Imperial, Los Angeles, Riverside, San Bernardino, San Diego, and Orange Counties. "Exotic Newcastle disease is a devastating bird illness that has the potential to wipe out the poultry industry", Davis said in a statement from Sacramento (55).

The U.S. Department of Agriculture announced on January 8, 2003, that it has expanded the quarantine boundaries for exotic Newcastle disease to encompass Los Angeles, Riverside, San Bernardino, San Diego, Santa Barbara, Ventura, Imperial, and Orange Counties in the State of California (147).

Exotic Newcastle disease is easily spread by people who have been around animals with the disease (142).

Officials say flock eradication is necessary to eliminate exotic Newcastle disease before it spreads to the heart of California's poultry industry, the Central California Valley (143).

California's chief veterinarian urged animal doctors to report any dead birds brought to their practices to an avian Newcastle disease eradication task force (141).

Big egg producers in Southern California have put their farms on virtual lockdown, barring visitors, washing down trucks, and disinfecting employees, to keep their birds safe from exotic Newcastle disease (145).

A task force battling a deadly avian disease in California is warning residents with infected birds to beware of scam artists claiming to charge less money than task force personnel to clean and disinfect backyards. Eradication task force workers don't charge for disinfecting backyards (50).

More than 1 million egg-producing hens were ordered destroyed by California state officials after finding new cases of a fast-spreading and deadly avian virus in San Bernardino and San Diego counties. Orange County, which has no poultry production, was added to the quarantine area to stop the movement of birds across the region. The Southland represents only a small fraction of the 280 million chickens and turkeys raised in California. Nearly all of the state's meat birds are found in the Central Valley (53).

Newcastle virus has led state officials to order the destruction of about 1.2 million chickens in recent weeks, and prompted the California Department of Food and Agriculture to draft a request to the governor for disaster assistance. The state's egg industry, which reached its peak of 42 million hens in 1971, when the last outbreak of exotic Newcastle virus hit, has since shrunk by half to about 22 million birds. The 1971 outbreak led to the destruction of 12 million birds at a cost of \$56 million (54).

To date, more than 1.7 million chickens have been infected by exotic Newcastle disease in San Bernardino County, and nearly 2 million birds in California have had to be killed because of the infection (138).

A San Bernardino County-owned landfill in North Rialto has accepted nearly 190 tons of chickens killed at egg ranches across the county as exotic Newcastle disease continues to spread among commercial and backyard flocks (138).

Exotic Newcastle disease has now spread to western Arizona, and was found in a flock of about 35 chickens at the Colorado River Indian Reservation, just east of the California border (141).

Newcastle virus has been found on four more commercial poultry farms within Southern California's quarantine zone, the most reported in a single day since the outbreak began more than four months ago. Of the latest infected farms, one was in Riverside County, two were in San Bernardino County, and another in San Diego County. These discoveries bring the total number of farms affected to 12, and the number of birds destroyed or slated for destruction to 2.4 million. To date, the outbreak has cost the state of California more than \$35 million to fight the disease and to compensate farmers for birds they are ordered to destroy. Agriculture

Secretary Ann Veneman has declared an “extraordinary emergency” in California, Nevada, and Arizona (63).

Exotic Newcastle disease has spread to a fourth commercial egg ranch in San Bernardino County. The ranch has 72,000 hens. San Bernardino County now leads all other counties with 779 infected sites. Statewide, more than 2 million birds have been destroyed to date, and more than 1,500 state and federal workers are fighting the disease. Its symptoms, which are fatal to birds, include respiratory and digestive system problems (140).

Fowl at a seventh commercial egg ranch in San Bernardino County have been found to be infected with exotic Newcastle disease. The ranch's 17,000 hens pushed the county's total of birds that have been or will be destroyed to more than 1.7 million. That is a significant portion of the estimated 4 million to 4.5 million egg-laying hens in the county. Eggs are San Bernardino County's fourth-largest agriculture commodity, bringing in about \$26.2 million a year (139).

San Bernardino County continues to have had the most cases of Newcastle disease, with 781 infected sites. Riverside County has had 527, Los Angeles County 237, and Clark County, Nevada, 91 (141).

In October 2002, Taiwan banned fresh/frozen poultry and poultry products originating from flocks, slaughtered or processed in California for 12 months beginning October 3, 2002 (146).

In December 2002 China banned poultry and poultry products originating from California produced after November 29, 2002 (146).

By year-end 2002, Japan had banned poultry and poultry products raised or processed in an area within a 50-km (31-mi) radius around the Newcastle-quarantine areas in the State of California (146).

Mexico has threatened a ban on all U.S. poultry products on concerns that the current outbreak of exotic Newcastle disease could spread to commercial poultry operations outside California. Mexico, the third largest export market for U.S. poultry producers, bought 123,000 tons, or \$63 million, of leg quarters in the first 10 months of last year. Mexico already has a prohibition on California poultry. Newcastle has spread to Clark County, Nevada, which was immediately quarantined by the state of Nevada. Mexico is the only major U.S. poultry buyer mulling over a ban on all poultry imports from the U.S. Two other big buyers, Russia and Canada, have limited their bans to California (56).

Mexico has threatened a ban on all U.S. poultry products on concerns that the current outbreak of exotic Newcastle disease could spread to commercial poultry operations outside California. A ban would shut off the third-largest export market for U.S. poultry producers. Mexico bought 123,000 tons, or \$63 million, of leg quarters in the first 10 months of last year. Mexico already has a prohibition on California poultry (144).

As of 2003, Mexico had in place bans on imports of California poultry and eggs (146).

As of January 2003, Canada placed a ban on all poultry meat, poultry meat products, hatching eggs, and live poultry from the State of California, including poultry and poultry products originating from birds raised, or processed in the State of California (146).

On January 28, 2003 the Council adopted a Decision to confine EU import restrictions of live poultry, hatching eggs, fresh poultry meat, and poultry products to the States of California, Nevada, and Arizona. Exports of those products had been suspended from the entire territory of the U.S. since October 2002 due to several outbreaks of Newcastle disease in California and Nevada (149).

In 2001, the combined value of production from broilers, eggs, turkeys, coupled with the value of sales from chickens, was \$24.0 billion, up 13% from \$21.2 billion in 2000. Of the combined total, 70% was from broilers, over 18% from eggs, over 11% from turkeys, and less than 1% from other chickens (151).

In 2002, U.S. exports of poultry broiler cuts totaled 1,978,256 metric tons, the leading importers being Russia (663,342 metric tons), Hong Kong (250,719 metric tons), and Mexico (134,085 metric tons) (148).

In 2002, U.S. exports of turkey cuts totaled 163,385 metric tons, the leading importers being Mexico (73,789 metric tons), Hong Kong (27,671 metric tons), and Russia (11,480 metric tons) (148).

In 2002, table egg exports totaled 43,614,000 dozen, the leading importers being Hong Kong (21,238,000 dozen), Canada (15,092,000 dozen), and Japan (1,721,000 dozen) (148).

Tyson, headquartered in Springdale, Arkansas, generated sales of \$23.4 billion during the fiscal year ended September 28, 2002. Tyson produces roughly one-third of the nation's chickens (44).

An outbreak of avian influenza is seriously affecting Italy's poultry industry in the Lombardy and Beneto regions, with almost a million birds being slaughtered in the past few weeks. Two years ago, some 14 million birds had to be killed following a chicken flu outbreak in the area. The current situation is regarded as "critical" since the virus is considered to be stronger and more resistant to cold (150).

Avian influenza, discovered over the weekend of March 1 in the Netherlands, for the first time in 30 years, has been found on 18 farms in Gelderland Province, in the center of the country, home to about one-third of the country's chicken population. Some 200,000 chickens and other poultry on 13 farms were expected to be slaughtered by late-night, March 5. Other cases are believed lurking, however, because the virus usually mutates from a low-virulent strain to a more powerful variety. The Netherlands, with around 100 million poultry, mostly chickens, is the world's fourth-largest poultry exporter and the largest in the European Union (179).

Dutch health officials said that people working with chickens involved in an outbreak of avian (H5N1) flu would be vaccinated against human influenza, to avoid the slim chance of the human and bird viruses combining (232).

The Hong Kong government ordered the immediate slaughter of 1.2 million chickens—virtually the territory's entire poultry population—in a drastic attempt to stamp out a chicken virus that officials feared could eventually affect humans. Authorities in Macao, about 40 miles west of Hong Kong across the Pearl River estuary, said they would destroy the territory's entire poultry stock of about 20,000 birds after detecting the same virus among chickens there. In 1997, the deaths of six people were traced to a different strain of the same chicken virus, called H5N1. About 1.4 million birds were ordered killed in a belated effort to avert a potentially far broader public health disaster in that instance (116).

A 33-year-old man who died in the second week of February, 2003, after visiting Fujian Province in southeaster China was infected with the avian flu virus. New news raises fears of another outbreak of the virus, which killed 6 people in Hong Kong in 1997, and prompted the slaughter of 1.4 million chickens (155).

In April 2003, two new suspected cases of the highly contagious bird flu were discovered in Belgian farms near the Dutch border. The disease has spilled over into Belgium from neighboring Netherlands, where some 11 million birds have been slaughtered since late February in an effort to control it (366).

After the death of a veterinarian from avian flu in April, the Dutch Ministry of Agriculture widened its efforts to prevent humans contracting the virus. The 57-year-old vet died of pneumonia after becoming infected with the bird virus while collecting samples on chicken farms for several days (367).

Dutch health officials said they were investigating the death of a Dutch veterinarian believed to be the first human victim of the current bird-flu epidemic that is spreading in parts of Europe (368).

Rabbits

Viral rabbit calicivirus disease (RCD), one of the most deadly diseases on earth, causes massive bleeding in the lungs, intestines, and liver, killing its victims with a day or two. It was discovered among rabbits in China in 1984. It has since spread to Asia, Australia, Europe, Mexico, and South America; and now to the U.S. It doesn't affect wild jack rabbits or cottontails or humans—just domesticated bunnies at the heart of the rabbit-breeding industry and rabbit shows. About \$10 million a year is sold in rabbit meat in the U.S., and another \$15 million a year in rabbits for research (81).

Pharmaceutical Markets

U.S. Pharmaceutical Market

Brand-name drugs account for about 90% of total spending and about three-fifths of prescriptions in the U.S. market (6).

The share of U.S. health-care dollars devoted to drugs rose to 11% in 1998, up from 8% in 1993 (8).

In 1992 the U.S. market accounted for only 34% of audited worldwide pharmaceutical sales; now it represents 50% and is expected to be worth \$330B in 2006 (17).

Prescription drug sales in the U.S. grew 12% to \$192.2 billion in 2002, up from \$172 billion in 2001. In 2001, sales grew 17% from 2000. Prescription sales in 2003-2004 are predicted to grow 10% to 11% annually, then increase again the following years to an average annual growth rate from 2002 through 2006 of around 12%. Essential to the industry's sales growth is its ability to raise drug prices by an average annual 4%—nearly double inflation (154).

Retail pharmacies sold 62% of all prescription drugs in the U.S. in 2002. But, mail-service sales grew 21% and now account for 13% of all U.S. prescription-drug sales (154).

In 2002, 51% of prescriptions filled in the U.S. were filled with generic drugs (154).

The U.S. is now the principal source of profits for most drug makers and U.S. consumers are increasingly bearing most of the costs for private drug research worldwide (154).

The highest selling drug in the U.S. in 2002 was Pfizer, Inc.'s cholesterol-reducer, Lipitor, with \$6.1 billion in U.S. sales. Merck's cholesterol-reducer, Zocor, was second with \$4.2 billion in sales (154).

The U.S. is the largest HIV drug market in the world (22).

The U.S. Market for AIDS and HIV therapeutics at the manufacturer's level was \$170 million in 1990 and \$255 million in 1995; and is estimated to reach \$515 million in 2005 (24).

The total U.S. market for AIDS drugs for the 12 months ending November 1999 was \$2 billion. The top sellers were: combivir (Glaxo-Wellcome, \$385.5 million), viracept (Agouron, \$377.7 million), zertec (Bristol-Myers, \$250 million), crivivan (Merck, \$166.8 million), and sustiva (DuPont, \$128.1 million) (167).

AIDS drug-assistance programs, or ADAPs, throughout the U.S. and its territories serve about 80,000 clients, about 30% of the U.S. market for AIDS drugs (175).

The U.S. Market for herpes virus therapeutics at the manufacturer's level was \$260 million in 1990 and \$665 million in 1995; and is estimated to reach \$1.2 billion in 2005 (24).

The U.S. Market for influenza therapeutics at the manufacturer's level was \$93 million in 1990 and \$105 million in 1995; and is estimated to reach \$117 million in 2005 (24).

A new class of flu drugs call neuraminidase inhibitors is expected to grow the total U.S. antiviral flu drug market from approximately \$25 million to \$80 million between the 1998-99 and the 1999-00 influenza seasons (108).

The value of the U.S. market for nutraceuticals is estimated at \$19.6 billion for 1999; and may top \$20 billion in 2000, constituting 10% of the total food market by 2010 (35).

The first new medicine in a new category—the breakthrough drug—is usually on the market just one to six years before therapeutically similar medicines are introduced (7).

About 85% of U.S. consumers currently (2002) spend more than \$17B annually on dietary supplements such as vitamins, minerals, herbs, and amino acids (14).

The nutraceuticals/dietary-supplement industry is currently about \$19 billion in the U.S. Forty to 60% of the U.S. population currently takes a vitamin or supplement (183).

International Pharmaceutical Markets

Pharmaceutical sales in 13 significant markets around the world rose 10% in the 12 months to the end of June, 2000 (9).

Sales through retail pharmacies in worldwide leading markets totaled \$216.2 billion in the 12 months to the end of June, 2000 (9).

The top 11 geographical markets for pharmaceuticals grew a combined 9% from October 1998 to October 1999, representing more than \$202 billion in sales (33).

Of the top 11 geographical markets for pharmaceuticals, the U.S. market grew the fastest at 14% year over year from October 1998, and was valued at \$83 billion. In comparison, Japan's market grew 6% to \$45 billion, whereas the combine growth rate of the top five countries of Europe (Germany, France, Italy, the U.K., and Spain) grew 7%, to \$54 billion (33).

In the 12 months to the end of June, 2000, North America remained the main driver of the global drugs business, with sales in the U.S. market—the world's biggest—rising 15% to \$91.2 billion and Canada recording its highest-ever growth rate of 17% to \$5.3 billion. Japan, the world's number 2 market at \$50.9 billion, showed 5% growth while the top five European markets grew by 7% to \$52.9 billion. Latin America reversed a recent decline in drug sales, expanding by 1% to \$12.9 billion (9).

In 2001, the global pharmaceutical industry was worth \$364.2 billion, a total from over 70 countries, and representing a 12% growth over 2000 (17).

Global prescription drug sales in 2001—\$364.2 billion—were dominated by North America (\$181.8 billion), followed by Europe (\$88.0 billion), Japan (\$47.6 billion), Asia, Africa, and Australia (\$27.9 billion), and Latin America (\$18.9 billion) (47).

North America (of which the U.S. comprises 95%) was the largest single market in 2001 at \$181.8 billion (50% of global sales); Europe was second (\$88.0 billion; 24%); Japan was third (\$47.6 billion; 13%); Asia, Africa, and Australasia ranked fourth (\$27.9 billion, 8%); while Latin America was fifth-largest (\$18.9 billion, 5%) (17).

In 2001, total pharmaceutical sales worldwide amounted to \$392 billion, which includes 90% of all prescription drugs (17).

Canadian research-based pharmaceutical companies will invest about \$1 billion in R&D in 2000 (7).

Half the difference in drug prices between the U.S. and Canada, on average, can be accounted for by tort liability risks in the U.S. (7, 18).

The global HIV drug market was valued at \$4.1 billion in 1998, representing an increase of 26.8% over sales of \$3.2 billion in 1997 (22).

Pharmaceutical Market Trends

Many smaller drug discovery and genomics-based biotechnology companies are beginning to move out of the laboratory and into the clinic, realizing that developing and marketing their own drugs is far more profitable and capable of driving sustainable growth than are licensing deals (17).

The sharp rise in U.S. health-care spending likely will slow during the next decade but will continue to outpace overall economic growth. National health-care spending—which grew by 8.7% to \$1.4 trillion in 2001—will grow at an average annual rate of 7.3% during the next decade, which will slow to 6.7% by 2012. Despite this, the health-care sector will still consume a growing portion of gross domestic product, reaching 18%, or \$3.1 trillion, by 2012 (40).

The Competition

Broad-Spectrum Antiviral Agents

Starpharma Pooled Development Ltd. (Melbourne, Australia) is developing dendrimers—large star-shaped polyvalent complexes of polyamidoamine, polylysine, and other polymeric molecules with multiple terminal groups bonded to an anionic- or cationic-containing moiety (U.S. patent 6,190,650)—which show promise for treatment of various viral diseases and as intravaginal microbicides (including against HIV). Unlike small-molecule drugs, polyvalent dendrimer complexes can interact with biological systems through simultaneous contacts, e.g., multiple receptor-ligand interactions. Polyvalent interactions collectively can therefore be much stronger than monovalent interactions (59).

Advanced Viral Research Corp. is developing a material called Product R, a non-toxic peptide nucleic acid (PNA) modulator, said to be a broad-spectrum antiviral drug that shows promise for the treatment of viral infections such as AIDS and HPV (109).

HIV-AIDS

The number of patients on HIV therapy, and the length of time for which they are on therapy, are both increasing, and are consequently driving a demand for HIV drug treatment (22).

The key factor driving the growth of drug treatment of HIV includes the recent adoption of combination therapies, whereby two, three, or even four antiretroviral drugs are taken together (22).

There were three major classes of HIV drug available in 1998. The leading class was the nucleoside reverse transcriptase inhibitors (NRTIs), with global sales of \$2.1B. Sales of the protease inhibitors (PIs) showed strong growth of 39.5% to \$1.8B. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) made up a small proportion of the market in 1998, despite sales growth of 125%, from \$72M in 1997 to \$162M in 1998 (22).

The leading NRTI in 1998 was Glaxo Wellcome's epivir, with sales of \$603M. However, epivir's sales were cannibalized by combivir, Glaxo's new combination treatment for HIV (combivir is a combination of lamivudine—3TC—the active ingredient of epivir, and zidovudine—AZT—the active ingredient of the company's other HIV drug, retrovir). Merck's PI, crixivan, was the leading HIV product globally in 1998, with sales of \$684M. The product is under increasing pressure from Agouron's recently launched PI, viracept, however, and sales are likely to decline over the next few years. Crixivan in fact lost its leading position in the U.S. market to viracept in 1998 (22).

By early 2000, the two best-selling protease inhibitor drugs, Merck's crixivan and Agouron's viracept, require patients to take six to 20 pills a day, divided over two or

three different times during the day. Taken together, AIDS "cocktails" can require patients to take as many as 30 pills a day (167).

The most recommended AIDS therapy in 2000 was a combination of a protease inhibitor plus two nucleoside analogs (71).

HIV protease inhibitors cause a panoply of side effects, including insulin resistance and even Type II (adult onset) diabetes. The drugs prevent a key glucose transport protein produced in fat and muscle cells, known as Glut4, from bringing glucose across cell membranes into the cells for energy storage (131).

Currently, 16 drugs are approved by the FDA to fight AIDS. Most are protease and reverse transcriptase inhibitors. At least a half-dozen more drugs are in human testing, with 10 or 12 more in the pipeline (88).

Protein-cleaving enzymes known as proteases are kept under tight control in nature because they are synthesized in vivo in an inactive form called a zymogen, which becomes active only after another protease cleaves a specific peptide bond. Zymogens might be engineered artificially to attack microbes, which may be a particularly useful strategy against retroviruses such as HIV and hepatitis C because they have RNA genomes (90).

At an AIDS research conference in San Francisco in February 2000, several pharmaceutical companies said they were attempting to improve the treatment of AIDS with new drugs, or versions of older medicines, that need be taken only once a day (167).

In the latest effort to trim the number of pills HIV-infected patients must take, the FDA approved Glaxo Wellcome PLC's trizivir, a combination of the company's AIDS drugs AZT, 3TC, and abacavir. Glaxo Wellcome also markets an AZT-3TC combination under the brand name combivir. Trizivir will cost \$26.60 a day (71).

While approving Glaxo Wellcome's newest AIDS drug trizivir (a combination of the company's AIDS drugs AZT, 3TC, and abacavir), the FDA also issued a stern warning regarding its use. About 5% of people who try abacavir (also known as ziagen) suffer serious, sometimes fatal allergic reactions (71).

A 2003 clinical trial of Glaxo SmithKline's AIDS drug trizivir was halted by NIH after it proved less effective than when used in combination with other AIDS drugs. Only 74% of patients still had a viral load of less than 200 after 48 weeks into the trial (170).

Glaxo SmithKline announced on April 28 that it would further reduce the price of Combivir, a key AIDS drug used in Africa and other parts of the developing world (363).

Merck has cut the price of its efavirenz HIV/AIDS medication for patients in the world's least-developed countries. The new price is 95 cents for a once-a-day 600-mg tablet, a 30% reduction from the price of the current three-capsule regimen and below the price offered by Indian generic drug companies (68).

Merck reported that they have found two experimental compounds that in laboratory tests were able to obstruct the activity of an enzyme called integrase, which plays a critical role when the AIDS virus infects cells (168).

A single dose of Boehringer-Ingelheim GmbH's AIDS drug, Viramune, administered to a woman just prior to giving birth, and a small dose of a syrup version of the drug given immediately to the newborn, can significantly reduce the risk of transmission to the child (73).

Data from tests of 600 patients followed for nearly two years showed that AIDS patients taking a drug cocktail containing Viread (Gilead Sciences, Inc., Foster City, CA) experienced less unexpected redistribution of body fat and saw lower rises in blood-serum cholesterol and triglycerides than patients on a similar cocktail containing stavudine (Zerit), a Bristol-Myers Squibb drug. A second study demonstrated that another, as-yet unapproved, Gilead HIV treatment called coviracil can be used effectively in a once-daily cocktail (89).

Pharmacia plans to license its AIDS drug, rescriptor (delavirdine), to generics manufacturers that would market a low-cost treatment only in the poorest countries. Pfizer is expected to acquire Pharmacia this quarter for \$55 billion (93).

Bristol-Myers Squibb announced in February 2000 that it was developing a powerful two-tablets once-daily protease-inhibitor drug (167).

AVI BioPharma and International Therapeutics will collaborate to develop AVI's neugene antisense compounds as HIV drugs, which are still in the preclinical drug-discovery stage of development (186).

If T-20 (Roche-Trimeris) receives approval, it will be the fifth class of anti-HIV drugs licensed for standard use (132).

Fuzeon is the first commercial drug in the fusion inhibitor class. All 16 currently approved AIDS drugs attack the virus after it has entered the human cell (4).

Fuzeon (T-20) (a polypeptide, said to act against HIV as a viral fusion inhibitor) is expected to be a useful therapy for patients who don't respond to other drugs (an estimated 50,000 patients in North America and Europe) (2).

Fuzeon (T-20) is a synthetic, linear 36-amino-acid polypeptide that mimics part of the gp 41 binding protein used by the AIDS virus to bind to receptor cells. It inhibits virus-to-cell and cell-to-cell fusion at nanomolar concentrations and has wide biodistribution, a bioavailability of 60% to 80% and a half-life of around 2 hours. A 100-mg dose yielded in one study a 1.5 log drop in HIV RNA over 14 days (121).

In each of two large-scale clinical trials, one group of patients was given a traditional mixture of AIDS drugs and a second group received a similar mixture plus fuzeon. In the first trial, 37% of fuzeon patients saw their virus levels drop below detectable levels, more than twice the rate of other patients (14%). Nearly all

of the 1,000 patients had shown resistance to other AIDS drugs before entering the study (62).

T-20 has a drawback in that it has to be injected under the skin twice daily, which may pose difficulties for use in some areas of third-world countries. Many recipients of T-20 also experience reactions at the skin site of injection (132).

An NDA was submitted to the FDA for fuzeon, which is expected to be Roche's only major new drug launch in 2003. It is expected to gross about \$330 million annually (75).

Fuzeon is difficult to synthesize, requiring 106 synthetic steps—more than 10 times the typical number of chemical reactions in drug manufacture (2).

Almost 100,000 pounds of specialized raw materials are needed to make little more than 2,200 pounds of Fuzeon (2).

The estimated cost of Fuzeon is between \$12,000 and \$17,000 per patient per annum, more than any other drug on the market (2).

Roche Holding AG of Switzerland said it won't be able to meet the full demand in 2003 for its new AIDS drug, Fuzeon. The amount of Fuzeon available by year-end 2003 will meet the needs of only 15,000 patients, well short of the 25,000 patients it originally projected. By 2004 capacity is expected to double to enough drug for 32,000 patients, with a projection of sufficient drug to treat 39,000 patients in 2005 (2,4).

Roche Holding AG said it will price its AIDS drug fuzeon in Europe at EU18,980 (\$20,424) for a year's supply, double the most expensive treatments on the market. The company says it has invested more than \$600 million in developing the drug (62).

Fuzeon, a viral fusion inhibition drug, received FDA approval in March, 2003 (169).

Fuzeon, a viral fusion inhibition drug, received FDA approval in March, 2003. Some doctors and researchers consider fusion-inhibition drugs such as fuzeon the biggest advance in AIDS treatment since the introduction of protease inhibitors in the mid-1990s. However, fuzeon carries a record-setting price—\$20,514 per patient per year in Europe; likely to be the same in the U.S., and more than double the most expensive treatments on the market (171).

T-1249 is a fusion-inhibition drug from Roche/Trimeris that is intended to be used when the AIDS virus grows resistant to T-20 (fuzeon). Other versions are in the design stage to take over when T-1249 fails (88).

As part of a topically-applied microbicide cream, nonoxynol-9 (nonylphenyl polyethylene glycol ether) was found to kill HIV in in-vitro testing, but recent studies have found that the compound actually may increase some microbes' infectivity (118).

Columbia Laboratories, Inc. (Miami, Florida) reported that its Advantage S vaginal spermicide unexpectedly failed to show any benefit after five years of testing among hundreds of prostitutes in Africa and Thailand (130).

Around the world, but especially in developed countries such as the U.S. and in Europe, as many as 78% of HIV patients on therapy are believed to carry viruses resistant to at least one common drug, while nearly a third no longer respond to two or three medicines (171).

Chief of the California Department of Health Services Office of AIDS estimates that 30% of the program's 25,000 AIDS patients show signs of resistance to at least one or two existing AIDS drugs (62).

Molecules identified by researchers at the University of Maryland, Baltimore County, bind to a novel target in HIV, thus opening a new line of attack on AIDS. The compounds disrupt the assembly of the HIV-1 capsid protein, which is a vital step in changing immature non-infectious HIV into its mature, infectious form (364).

Herpes Viruses

Eli Lilly & Co. and 3M Co. suspended clinical trials of their genital herpes treatment, resiquimod (a more potent sister to 3M's alidara), because preliminary data showed the drug wasn't as effective as expected (61).

Eli Lilly & Co. is developing a family of immune-response modifier drugs (IRMs) for genital herpes. The drugs are said to be a broader class of compounds than resiquimod, which recently was withdrawn from clinical trials because of less-than-expected efficacy (61).

Glaxo Wellcome began a Phase III clinical trial of valacyclovir for reducing the transmission of genital herpes (usually attributed to HSV-2) (26).

In a 2002 study, herpes simplex virus was isolated from 2088 of 3602 patients; 90.2% of isolates were HSV-2. Fifteen isolates, all HSV-2, were acyclovir-resistant. Three of 1644 HIV-negative patients had acyclovir-resistant isolates. Twelve of 226 HIV-positive patients yielded resistant HSV isolates (162).

Denavir is a new topical cream for herpes viruses; it reduces the length of time for healing of herpetic lesions from 5 days to 4.5 days. It exhibits minimal benefit. Valacyclovir (valtrex), famciclovir (famvir), and acyclovir (zovirax) are equivalent drugs, with about the same efficacy (103).

BILS 179 BS, developed by Boehringer-Ingelheim, is said to be effective against skin and vaginal lesions in animal herpes models (119).

BAY 57-1293, a compound developed by Bayer, is said to hasten the healing of herpes lesions in animal models (119).

Both of the above compounds work by acting on two enzymes, helicase and primase, that are part of an enzyme complex HSV needs to untwist its double-stranded DNA

to form single strands and then prime the strands for replication into new viral DNA. By contrast, acyclovir, the traditional treatment for herpes simplex, targets DNA polymerase, the enzyme that acts on the primed single strand (119).

Avanir Pharmaceuticals concluded an agreement with SmithKline Beecham Corp. in December 1999 granting the company exclusive over-the-counter (OTC) or non-prescription marketing rights to docosanol 10% cream for topical treatment of oral-facial herpes (HSV-1). Docosanol cream will become the first OTC antiviral drug marketed in the U.S. (27).

An experimental vaccine from Glaxo SmithKline prevented infection in 74% of women exposed for the first time to genital herpes virus (simplex type 2), but the vaccine didn't work at all in men. The vaccine also didn't work well in women who had previously been infected with simplex virus type 1, which is responsible for cold sores or fever blisters (99).

A SmithKline Beecham herpes simplex type 2 vaccine reduced the risk of women developing genital herpes by 75% (114; see also 99).

Lysine is thought to suppress herpes simplex type 1 virus by increasing the ratio of lysine to arginine. High doses of lysine, 1,000 to 3,000 milligrams per day, are typically taken for a short period of time to control a herpes outbreak (100).

Penciclovir 1% cream is indicated for treating herpes zoster and recurrent labial herpes simplex infections in adults. It reduces healing time only slightly, and must be applied very 2 hours during waking hours for 4 days (104).

HPV

Aldara (imiquimod) cream, 5% is the newest in a class of HPV drugs called immune response modifiers (action unknown), and represents the first new therapeutic approach to genital warts in five years. (101).

Aldara, when applied topically, works by inducing the production of interferon and other cytokines. It is applied 3 times weekly for 16 weeks; the overall cure rate is only 50% (72% in women, 33% in men) (102).

Currently, no available treatment effectively eliminates warts, genital HPV infection, or replication (101).

Influenza

Older flu drugs include amantadine and rimantadine, but those drugs work only against influenza type A, typically the more common flu strain (98).

The older flu drugs can cause drowsiness (98).

The influenza drugs amantadine and rimantadine are both associated with higher levels of adverse effects than zanamivir, are effective only against influenza A, and have never been widely prescribed in the U.S. (20).

On July 27, 1999, the FDA approved zanamivir (from Glaxo Wellcome) for the treatment of influenza. Zanamivir is the first inhibitor of the influenza virus neuraminidase enzyme (a viral enzyme required to break the bond holding new virus particles to infected cells) to enter the market; the first drug to receive approval for treatment of infections with both influenza types A and B; and the first antiviral drug administered as a powder for inhalation (10 mg of powdered drug twice daily for five days). It is the first drug to receive FDA approval for influenza indications since the approval of rimantadine in 1993 (20).

The new class of flu drugs call neuraminidase inhibitors is expected to grow the total U.S. antiviral flu drug market from approximately \$25 million to \$80 million between the 1998-99 and the 1999-00 influenza seasons (108).

By preventing neuraminidase function and the separation of virus particles from infected cells, zanamivir prevents the release of new virus and further infection of the respiratory tract (20).

Zanamivir reduces the duration of influenza-related symptoms for perhaps up to several days. This level of efficacy is roughly comparable to that of influenza drugs already on the market, oral amantadine from DuPont Merck Pharmaceuticals and oral rimantadine HCl from Forest Laboratories (20).

Two new flu drugs, tamiflu from Hoffmann-La Roche and Glaxo SmithKline's relenza, a powder taken through an inhaler, can help relieve both influenza A and B viruses, with fewer side effects (98).

Glaxo Wellcome's flu drug relenza and Hoffman-La Roche's drug tamiflu are now awaiting market approval. Both drugs are part of a family known as neuraminidase inhibitors and are effective in treating type A and type B flu viruses—unlike older flu drugs, which fight only type A (110).

Hoffman-La Roche submitted a new indication application to the FDA for its influenza-antiviral drug tamiflu, to be used in children age one year and older. According to the company, tamiflu reduced the duration of influenza by 26% in children one to 12 years old when given within two days of symptoms' onset (107).

Tamiflu can cause upset stomachs about 10% of the time (98).

Because relenza used an inhaler, it can't be used by young children or by people with underlying asthma or respiratory problems (98).

The newer flu drugs can be expensive, costing as much as \$50 for one round of treatment (98).

SARS

As many as a thousand drugs already licensed for other viruses are being screened at Ft. Detrick, Maryland, to see if any might combat coronaviruses (249).

Marc Collett, ViroPharma's vice president of discovery research, warned that designing a new custom-made drug for SARS or any emerging virus is a five year program (249).

Patrick Iversen, chief scientist at AVI BioPharma, Inc (Portland, Oregon) has developed a drug technology known as "antisense" (a way of building genetically targeted drugs using DNA-like material) that may show some efficacy against SARS. In theory, antisense drugs can be designed and produced in days instead of the years that conventional pharmaceuticals usually require (250)

AIDS researcher David Ho said he has agreed to conduct work on potential therapy and vaccine approaches for SARS. He stressed that most of those strategies would take years to bear fruit (245).

CDC warned that a vaccine to protect against SARS remains at least a year away (246).

As scientists work to pinpoint the cause of the mysterious new respiratory illness, doctors on the front lines are debating how best to treat it. Officials at WHO and CDC say no definitive treatment for SARS has yet been found. Ribavirin together with steroids is generally used for the most seriously ill patients (270).

As SARS began infecting hundreds of patients some six weeks ago, Hong Kong's medical community improvised a treatment combining the antiviral drug ribavirin with corticosteroids, which act as an anti-inflammatory. Recent spikes in SARS deaths, however, are raising doubts about the efficacy of the treatment (306).

Doctors in Canada have stopped using ribavirin to treat most patients suffering from SARS because health officials believe the drug isn't effective in combating the disease (327).

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