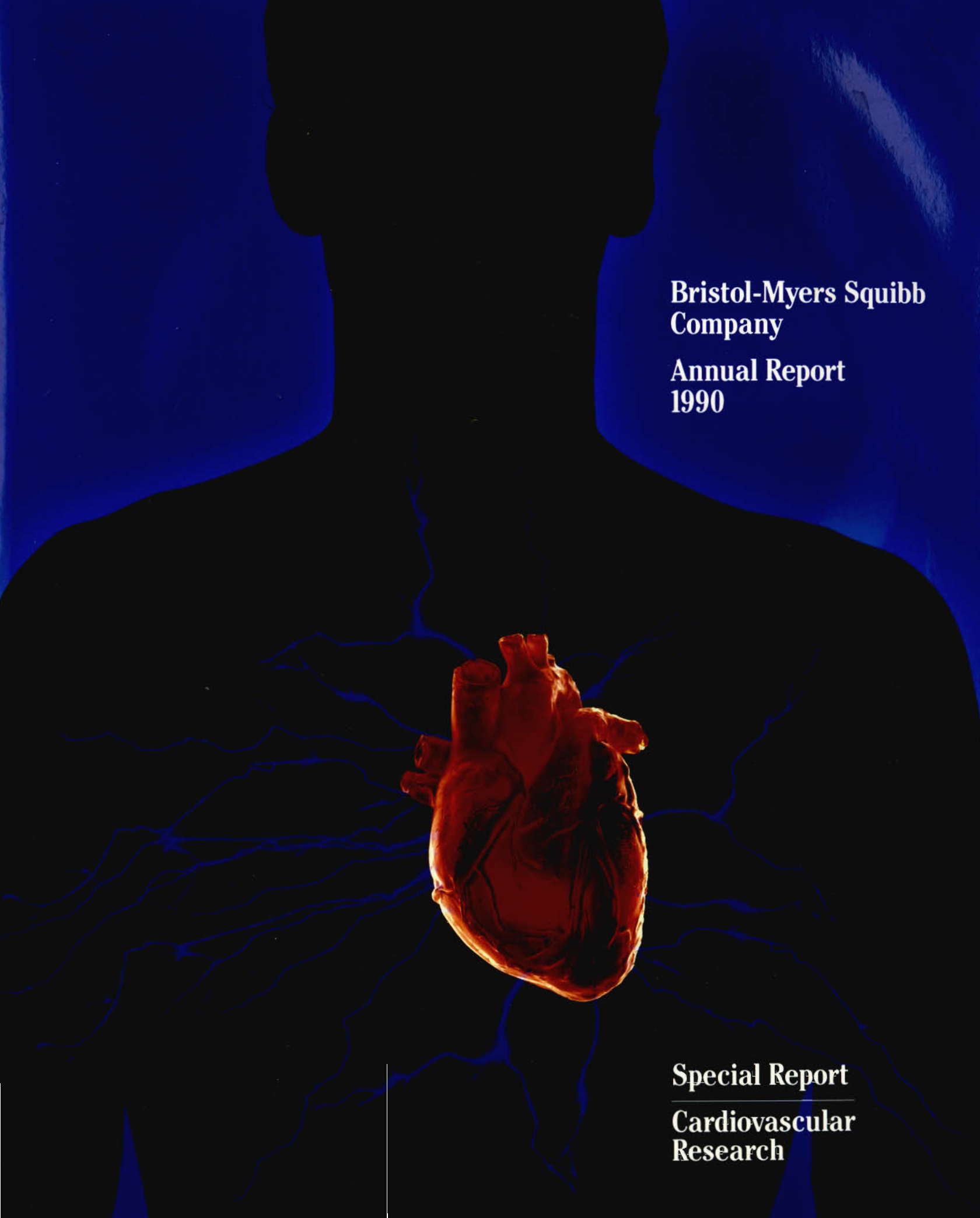


Bristol-Myers Squibb Company

Annual Report 1990

Special Report

Cardiovascular Research

Financial Highlights

Bristol-Myers Squibb Company

(in millions of dollars except per share amounts)	1990	1989*
Net sales	$10,300	$9,189
Provision for integrating businesses	—	$ 855
Earnings before income taxes	$ 2,524	$1,277
Net earnings	$ 1,748	$ 747
Earnings per common share	$ 3.33	$ 1.43
Dividends per common share	2.12	2.00
Working capital	$ 2,849	$2,893
Capital expenditures	526	562
Book value per common share	10.34	9.67
Number of employees	52,900	54,100
Stockholders of record	98,913	89,924

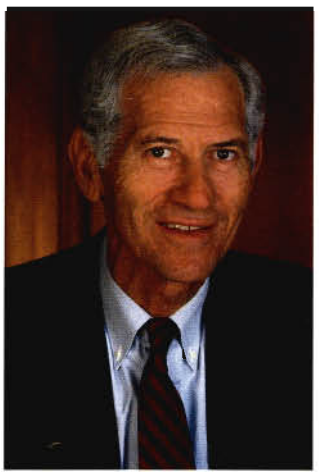
*The after-tax effect of the provision for integrating businesses was $693 million.

On the cover:

Cardiovascular disease is the leading cause of death in the developed world. A Special Report on Cardiovascular Research begins on page 14.

Contents:

Letter to Stockholders



Richard L. Gelb
Chairman and Chief Executive Officer

Nineteen ninety once again was a record year for Bristol-Myers Squibb Company, with particularly strong performances from our pharmaceutical, medical device and nutritional businesses. Our worldwide consumer products business was at the prior year's level with many individual brands performing well.

Worldwide sales increased 12 percent to $10,299,729,000, compared with $9,189,147,000 in 1989. Net earnings increased to $1,747,703,000. Excluding the 1989 charge of $855 million for integrating operations and for merger-related expenses, 1990 earnings before income taxes increased 18 percent, and net earnings increased 21 percent. Earnings per share reached a record high of $3.33.

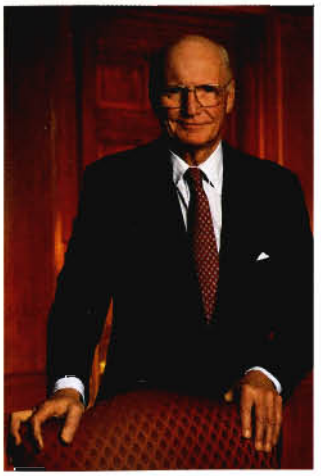
Dividends per common share were $2.12, a 6 percent increase over the $2.00 paid in 1989. An additional dividend increase was announced in December. The 1991 indicated annual payment of $2.40 represents a 13 percent increase over the $2.12 paid in 1990. With this 1991 payment, Bristol-Myers Squibb dividends will have increased at a compound annual rate of 18 percent over both the past five years and the past ten years. During 1990, 9.5 million shares of Bristol-Myers Squibb common stock were repurchased by the company.

We are pleased to report that our profit margins in 1990 were the highest in our history. Return on shareholders' equity reached a record 33 percent.

We continued to invest in future growth. Research and development expenditures increased 12 percent to $881 million. Advertising and promotion support increased to $1.3 billion.

Domestic sales increased 7 percent, and international sales increased 20 percent. Favorable exchange rate fluctuations increased total company sales growth by approximately 2 percent.

We are proud of what we have accom-



Richard M. Furlaud
President

plished during 1990. Yet we see those results as just a good beginning, an early indication of the excellent prospects that lie ahead for our company.

We have completed our first full year as Bristol-Myers Squibb Company. Following our merger in October 1989, we moved quickly to integrate and consolidate our operations around the world. In March, we consolidated management of our worldwide pharmaceutical research and development operations with the creation of the Bristol-Myers Squibb Pharmaceutical Research Institute. We are off to a good start on the merger integration process.

As a company, we remain strongly committed to growing each of our four core businesses, both through internal growth and through acquisition. Bristol-Myers Squibb Company today has 22 products—including 11 pharmaceuticals, six consumer product brands, two nutritional products and three medical devices—that enjoy over $100 million each in annual sales worldwide. These results indicate the strong balance and diversity of our businesses, strengths that have allowed our company to grow so consistently through the years.

The medical device business achieved strong growth during 1990. In June, we completed the acquisition of the *Concept* arthroscopy products business. Arthroscopy products, in which surgeons use fiber optic technologies and specialized instruments to visualize and repair joints, comprise one of the fastest growing segments of the orthopaedic market. Some 80 percent of arthroscopic procedures are performed on an outpatient basis, which are much less invasive than traditional open surgeries. In most cases, recovery time is cut in half or better. Some one million arthroscopy procedures are performed annually in the U.S. alone.

During 1990, the company also strengthened its position in the German implant market with the acquisitions of Orthoplant GmbH and S+G Implants GmbH, manufacturers of hip and knee implants.

Zimmer is the world leader in the reconstructive implant market. The *Miller/Galante* Total Knee System, the world's largest seller, was improved with the release in 1990 of the *MG II* Precoat Total Knee System, which incorporates more sophisticated instrumentation and a wider range of sizes. The *Zimmer Total System* remains the most widely used artificial hip system in the world.

Our ConvaTec division expanded its leadership position in the worldwide ostomy market during 1990. Growth was particularly strong in the one-piece market segment, where the *Active Life* product line achieved outstanding growth. New *DuoDERM* wound care products have been introduced in a number of markets around the world, continuing to provide innovative wound management for patients with leg ulcers, pressure sores, post-operative wounds and burns.

During 1990, we made an important move to strengthen our worldwide consumer products business for the long term, particularly nonprescription pharmaceuticals. Currently, more than 80 percent of our consumer products sales are in North America. In December, we completed the acquisition of a significant minority interest in the UPSA Group of Rueil-Malmaison, France, the largest privately-held self-medication drug company in Europe and a leader in analgesics in France. The agreement also gives Bristol-Myers Squibb Company the opportunity to acquire the remaining shares of UPSA in the longer term, subject to French government approval.

The UPSA Group is well recognized for its innovative products, technology and research and will provide added strength to our over-the-counter consumer products business and provide an important foothold in Europe. This partnership also offers us an important opportunity to work with UPSA in developing its products on a worldwide basis, particularly in the U.S. and Japan, where we already have strong positions in the nonprescription marketplace.

"We are pleased to report that our profit margins in 1990 were the highest in our history."

"We are proud of what we have accomplished during 1990. Yet we see those results as just a good beginning..."

Consumer businesses in Japan, Greece, Taiwan and Thailand all achieved strong growth during 1990. *Mum* became the leading deodorant in Spain for the first time during 1990. *Bufferin* became the number one brand of oral analgesics in Japan in 1989 and continues to increase its share of the market there. In May, Bristol-Myers Products launched Aspirin Free *Excedrin* in the U.S.

Major Clairol brands achieved good growth. *Nice 'n Easy*, the leading permanent haircoloring in the U.S., celebrated its 25th anniversary during 1990 with record sales. *Nice 'n Easy* is an example of the power of well established consumer brands to produce reliable earnings over many years. *Motif* gel haircoloring was introduced in Mexico, and a number of new haircolorings and hair care products were launched in Greece, Thailand and other markets.

Our important *Renuzit* and *Windex* household product lines continued to set new records. Early in 1991, Drackett introduced *Renuzit* Fragrance Jar, a new entry in the highly competitive air freshener market. The *Mr. Muscle* line of household products achieved strong sales in the U.K. and Australia.

Enfamil remains the company's largest selling nutritional product and the second most popular brand of infant formula in the U.S. Sales of Gerber Baby Formula continued to show excellent growth. During 1990 several new nutritional products were introduced including *Ricelyte*, a new rice-based oral electrolyte solution for pediatric use.

International infant formula sales also continued to grow well in 1990. Routine infant formula sales have benefited in France and Spain from the introduction of ready-to-use product forms.

Our pharmaceutical business was the greatest contributor to growth during 1990. With cardiovascular disease a leading cause of death around the world, innovative research and breakthrough pharmaceuticals to treat this disease are vital. Some remarkable advances in the field are being made and new knowledge is being gained every day. A Special Report on Cardiovascular Research begins on page 14.

Capoten, our leading ACE inhibitor, demonstrated remarkable resilience in the face of an increasingly competitive marketplace, achieving strong sales growth. This is the result of increasing acceptance worldwide for use of *Capoten* in the treatment of hypertension and early in the treatment of heart failure. Co-promotion efforts also have helped bolster *Capoten* sales. This year, the *Capoten* product line took over the leading position in the German hypertension market. Our second generation ACE inhibitor, *Monopril*, with its convenient once-a-day dosage, is now awaiting regulatory approval in the U.S. and other major markets, and is already being marketed in the United Kingdom as *Staril*.

Relatively few of the many millions of people around the world who have high cholesterol levels that might benefit from drug therapy are currently receiving such treatment. We expect that the market will expand significantly over the next few years with the approval of new lipid-lowering agents.

In October, the U.S. Food and Drug Administration's Endocrine and Metabolic Advisory Committee recommended that *Prava*, the company's new cholesterol-lowering drug, be approved for marketing in the U.S. It is already approved and being marketed in a number of countries, including Germany, France, Canada, the U.K. and Italy. We expect that *Prava* will become an important contributor to future growth. Sales of *Questran*,

Left to right:
Charles A. Heimbold, Jr.
Executive Vice President
Michael E. Autera
Executive Vice President
Wayne A. Davidson
Executive Vice President

another lipid-lowering agent, continued to grow.

In late December, the FDA approved *CardioTec*, a diagnostic imaging agent for use in diagnosing coronary artery disease. A significant advantage of *CardioTec* over other agents is that cardiac function can be measured more quickly. *CardioTec* joins *CardioGen-82*, which received FDA clearance in late 1989 as the first radiopharmaceutical approved for use with PET (positron emission tomography) scanners, to help diagnose cardiovascular disorders. *Isovue*, the company's nonionic diagnostic contrast medium used in a wide variety of cardiology and radiology applications, continued to achieve strong growth in the U.S. and Canada.

The development of effective therapeutic agents to treat AIDS (Acquired Immune Deficiency Syndrome) and AIDS-Related Complex remains one of our company's top pharmaceutical research priorities. In September 1989, we embarked on an expanded access program, in which patients who could not take AZT, the only approved antiviral agent against AIDS, would be eligible to receive our own compound, *VIDEX* (ddI), without charge. At the same time, we initiated an extensive series of clinical trials in a number of countries to test the efficacy of *VIDEX* in increasing the immune response of AIDS patients and in interfering with the replication of the AIDS virus. We plan shortly to submit our request to market *VIDEX* to the FDA and regulatory authorities in other countries. Approximately 16,000 patients have now taken *VIDEX* as part of the expanded access and clinical trial programs. Our research scientists also are working on additional anti-AIDS drugs and have several promising candidates in the research pipeline.

We filed a New Drug Application (NDA) in March seeking approval from the FDA to market cefprozil, an oral cephalosporin antibiotic with a broader range of activity and greater dosing convenience than other similar antibiotics. An NDA for cefepime, an injectable antibiotic with an extended spectrum of activity, will be filed later this year. Sales of our cephalosporin antibiotics, including cefadroxil, marketed as *Duricef* in the U.S. and as *Oracefal* in France, were strong. In the U.S., sales benefited greatly from favorable rulings by the U.S. District Court of Appeals and the International Trade Commission that upheld the company's patent for crystalline cefadroxil monohydrate, prohibiting the importation of cefadroxil which infringes the company's valid patent until the year 2002.

Our line of anti-cancer agents continued to perform extremely well. *Paraplatin* was launched in May in Japan for use against a broad range of cancers and continues to find growing use in outpatient therapy for ovarian cancer. *VePesid* experienced significant growth in 1990 and continues to be used in treating a broad spectrum of tumors. In September, we filed an NDA with the FDA seeking approval to market teniposide, an anti-cancer agent for use against acute lymphocytic leukemia. Teniposide is currently marketed outside the U.S. as *Vumon*. In late January 1991, we signed a Collaborative Research and Development Agreement with the National Cancer Institute for clinical development of taxol, a novel compound that has shown promising anti-tumor activity in several clinical trials.

BuSpar, our novel anti-anxiety agent, continues to show impressive growth, with particularly strong sales in France, as well as in the U.K., where it is now the leader in the anti-anxiety market. Its sales in the U.S. passed the $100 million level for the first time in 1990, reflecting increasing physician acceptance of this breakthrough product. *BuSpar* continues to be the fastest growing major anti-anxiety drug on the market, offering effective relief of anxiety without the adverse side effects of other widely-used anti-anxiety agents. We expect to file an NDA for approval to market nefazodone, our new antidepressant, later this year.

In August, Westwood Pharmaceuticals, our dermatology division, changed its name to Westwood-Squibb Pharmaceuticals, reflecting the integration of Squibb prescription dermatologicals into Westwood's line. In late December, the FDA approved *Ultravate*, an ultra-high-potency topical steroid for treatment of moderate to severe dermatosis. *Lac-Hydrin*, a prescription lotion used to treat severe dry skin and a scaly condition called ichthyosis, was

"As a company, we remain strongly committed to growing each of our four core businesses, both through internal growth and through acquisition."

"The development of effective therapeutic agents to treat AIDS and AIDS-Related Complex remains one of our company's top pharmaceutical research priorities."

joined by *Lac-Hydrin Five*, a moisturizer available without a prescription for moderate dry skin.

On January 1, 1991, William R. Miller retired as vice chairman of the board and a director of Bristol-Myers Squibb Company after 26 years of outstanding service to the company. In his distinguished career he has made many contributions to our company's success. He has also played a vital leadership role in the pharmaceutical industry at a time of unusual challenge.

Since publication of our last annual report, Wayne A. Davidson, executive vice president and a director of the company and president, Bristol-Myers Squibb Pharmaceutical and Nutritional Group, has assumed additional responsibility for the Bristol-Myers Squibb Pharmaceutical Research Institute and is now in charge of our entire pharmaceutical business.

Edgar Haber, M.D., a director of the company, was named president, Bristol-Myers Squibb Pharmaceutical Research Institute. Raymond C. Egan now has responsibility for the company's U.S. pharmaceutical and worldwide nutritional business. Kenneth E. Weg is responsible for the company's pharmaceutical business outside the U.S. Andrew G. Bodnar, M.D., was named senior vice president, strategic management, Bristol-Myers Squibb Pharmaceutical Group, succeeding William T. Comer, Ph.D., who retired after 29 years of distinguished service and many important contributions. Bruce R. Ross was named president, Bristol-Myers Squibb U.S. Pharmaceutical Group, and James J. Mauzey became president, Bristol-Myers Squibb U.S. Pharmaceutical Division.

Marvin H. Koslow was named president, Consumer Products Group; Thomas L. Dahl was appointed president, Drackett; and Richard F. Gaccione was named president, Bristol-Myers Products, replacing Stephen E. Bear, who was appointed senior vice president, strategic planning, Consumer Products Group.

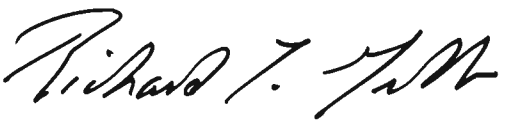
Frederick S. Schiff was appointed vice president and controller; Thomas D. McCann was appointed vice president, public affairs; and John D. Borgia, Victor J. Davis, José M. de Lasa, John T. Kirkland and Charles G. Tharp were appointed vice presidents, corporate staff.

Thomas H. Hughes retired as president, Bristol-Myers Health Care Group, after 26 years and Abramo Virgilio, Ph.D., president, technical operations, retired after 22 years. Senior vice presidents Joseph E. Maroun, with 30 years of service, and Julius L. Pericola, with 40 years of service, and vice presidents Isaac Jarkovsky, with 22 years of service, and Giulio Vita, Ph.D., with 15 years of service, also retired. All of these executives had distinguished careers with the company and we are indebted to them for their many contributions.

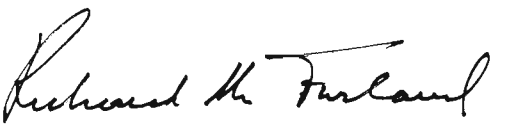
We want to express our sincere appreciation to Ray C. Adam, retired chairman of NL Industries, for his dedicated service as a member of the company's Board of Directors for the past decade. Mr. Adam retired from the Board as of May 1, 1990.

That we have achieved so much in this first full year following the merger is a testament to the skills, dedication, determination and hard work of the more than 50,000 Bristol-Myers Squibb employees around the world. We are confident that we will continue to achieve our business goals, contributing both to our company's future growth and to the important needs of society.

We are grateful to all our employees and stockholders for their continued support.



Richard L. Gelb
Chairman and Chief Executive Officer



Richard M. Furlaud
President

February 14, 1991

Major Business Developments Of the Year

In December, Bristol-Myers Squibb acquired a significant minority interest in the UPSA Group of Rueil-Malmaison, France, and will cooperate with UPSA to develop their product line in selected markets worldwide. The company, subject to French government approval, also will have the opportunity to acquire the remaining shares of UPSA in the longer term. UPSA is the largest privately-held self-medication drug company in Europe.

A new $80 million pharmaceutical plant was opened in Mayaguez, Puerto Rico, in April. The highly automated 230,000 square foot facility will turn bulk pharmaceutical products into finished products ready for sale in both U.S. and international markets.

Cardiovascular Research Center Funded; Genetic Research Supported

The company announced in May that it will provide more than $35 million over five years to fund a new Cardiovascular Research Center at Massachusetts General Hospital. The Center, to open in 1991, is expected to expand molecular and genetic approaches to cardiovascular biology, disease and treatments. Also in May, the company announced a $5 million award to support basic research over a five-year period on the genetics of development of disease at the Samuel Lunenfeld Research Institute of Mount Sinai Hospital in Toronto, Canada.

New Pharmaceuticals Introduced

New pharmaceuticals introduced around the world during the past year included:

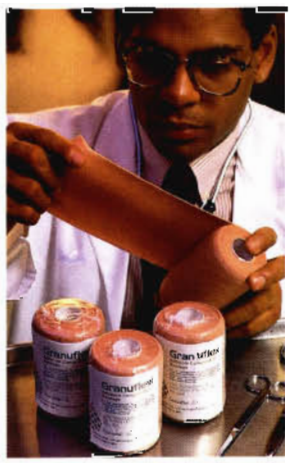
—*Monopril* (fosinopril), a new once-a-day ACE inhibitor, approved in the U.K. in July and launched in February, 1991 as *Staril*;

—*Prava* (pravastatin), a new once-a-day HMG Co-A reductase inhibitor, launched in several countries including France, Germany, Ireland, Italy, the Netherlands, the U.K., Mexico and Canada, and marketed under a number of different trademarks;

—*Paraplatin*, an anti-cancer agent, in Japan;

—*CardioTec*, first in a new class of diagnostic imaging agents, approved in the U.S.;

—*Ultravate*, an ultra-high-potency topical steroid, also approved in the U.S.



***Granuflex* Hydrocolloid Compression Bandage,** used to treat venous leg ulcers, was introduced in the U.K. in April. The special hydrocolloid adhesive helps the bandage maintain its compression and stay in place.

Goodwill Games/Olympics Sponsorships

● Bristol-Myers Products and Clairol were official sponsors of the 1990 Goodwill Games, held July 20–August 5 in Seattle, Washington. In July, *Nuprin* joined the 1992 United States Olympic Team as its official pain relief sponsor and Clairol announced that it will be the Team's exclusive hair care sponsor.

Bristol-Myers Squibb Pharmaceutical Research Institute Established

● In March, the company announced the establishment of the Bristol-Myers Squibb Pharmaceutical Research Institute, headquartered in Princeton, New Jersey. The Institute combines the former Squibb Institute for Medical Research, in Princeton, the Bristol-Myers Pharmaceutical Research and Development Division, in Wallingford, Connecticut, and Oncogen, in Seattle, Washington, into one organization with some 18 facilities and nearly 4,000 scientists and support personnel around the world.

▲ **New Nutritional Products Introduced**

New nutritional products launched during the past year included:

In the U.S.:

—*Ultracal*, the first nutritionally complete tube feeding product with a blend of oat and soy fiber;

—*Ricelyte*, the first rice-based oral electrolyte solution for use in infants and children suffering from diarrhea.

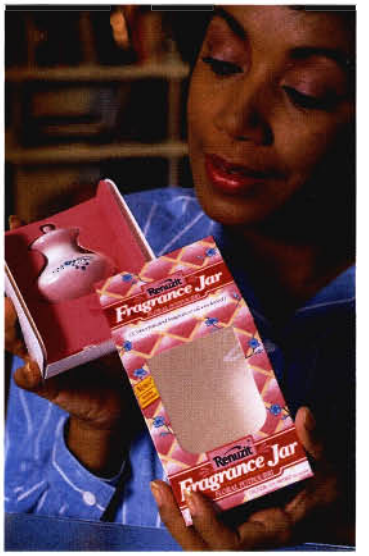
In Canada:

—*Boost*, a nutritional supplement or meal replacement product especially suitable for busy people, seniors, or for people needing extra nutrition.

Sustagen Junior, a popular nutritional supplement for children ages one to five, was introduced in a number of markets including Malaysia, Singapore and Hong Kong.

Iso Flo tube feeding system for *Isocal RTU*, a complete, ready-to-use tube feeding diet, was introduced in several markets including Malaysia, Singapore, France, Spain and Taiwan.

▲ **The anti-cancer drug *Paraplatin*** was launched in Japan in May and became the first major drug to be marketed in Japan exclusively by Bristol-Myers Squibb Company. In Japan, *Paraplatin* has been approved for use in small cell lung cancer, head and neck cancer, cervical, testicular and ovarian cancers and malignant lymphomas. Side effects with *Paraplatin* are fewer and less severe when compared to other cytotoxic agents.



▲ ***Renuzit* Fragrance Jar,** introduced in January, 1991, and packaged in an attractive ceramic container, is a new entry in the competitive air freshener market.

Divestitures

● Genetic Systems Corporation was sold to Sanofi, Inc., in April.
—The Squibb animal health business was sold to Ciba-Geigy Limited in April. The rights for Western Europe had been sold to Ciba-Geigy in 1984.
—The company's laundry products business in Canada was sold to the Colgate-Palmolive Company in April.
—The Jobst Institute, of Toledo, Ohio, and its Irish subsidiary, were sold to Beiersdorf AG in August.

Company Increases Dividend 13 Percent

● In December, the Bristol-Myers Squibb Board of Directors voted to increase the quarterly dividend on common stock by 13 percent to 60 cents per share.

▲ **Aspirin Free *Excedrin,*** the company's newest non-aspirin product, was introduced in the U.S. in May.

▲ **Over-the-Counter Products Introduced**

New over-the-counter products launched over the past year in the U.S. included:
—*Lac-Hydrin Five,* a nonprescription moisturizer for moderate dry skin;
—*PreSun* Spray Mist;
—*Excedrin P.M.* Liquid, the only liquid analgesic that combines an extra strength dose of acetaminophen for pain, with an ingredient for sleeplessness;
—*Ban* Body Fresh Scent anti-perspirant deodorant;
—Aspirin Free *Excedrin,* a new extra strength analgesic containing acetaminophen;
—Therapeutic *Mineral Ice*–Exercise Formula.
In addition, Children's *Bufferin* Multi-Symptom Cold Syrup was launched in Japan and *Girl's by Mum* anti-perspirant deodorant roll-on was launched in Mexico.

▲ **Clairol Shade Selector Computers in Retail Outlets**

Special computers, designed to answer consumer questions about haircolorings in order to introduce new users to the market, were installed in more than 4,000 retail outlets around the U.S. by early 1991. The Clairol Shade Selector Computers recommend a haircoloring shade based on responses to questions posed by the computer in English or Spanish.

FDA Committee Recommends Pravastatin Approval

● The U.S. Food and Drug Administration's (FDA) Endocrine and Metabolic Advisory Committee in October recommended pravastatin (*Prava*), the company's cholesterol-lowering drug, for approval in the United States. Pravastatin already is being marketed in a number of countries outside the U.S. and was introduced over the past year in France, Germany, Ireland, Italy, the U.K., the Netherlands, Canada and Mexico.

▲ **New Ostomy and Surgical Products Launched**

New ostomy and surgical products launched over the past year included:

—*DuoDERM* Adhesive Compression Bandage (in the U.S., Canada, Scandinavia and the Netherlands, and in the U.K. and Ireland as *Granuflex*);

—*DuoDERM* Extra Thin CGF Dressing (in Australia, Belgium, Italy, the Middle East, New Zealand, Scandinavia, France, Latin America, the Netherlands and Germany);

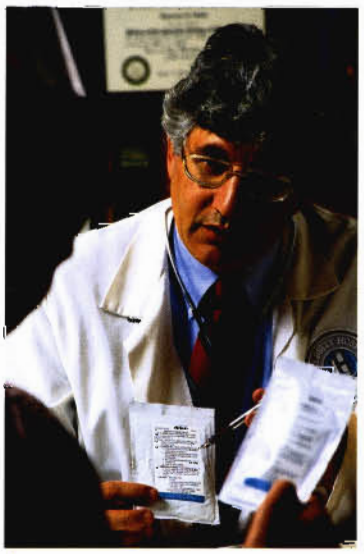
—*Active Life* Convex Urostomy Pouch (in the U.S. and Canada);

—*Ileodress Plus*, a one-piece drainable pouch for ostomy patients (in France and Germany);

—*Stomahesive* Flexible Flange, a bodyside wafer for ostomy patients (in the U.K.);

—*Laser Shield II*, a laser-resistant endotracheal tube (in the U.S.).

▲ ***PreSun* Spray Mist,** introduced in March, offers 23 times as much protection from the harmful effects of the sun's UVB rays as bare skin would provide.



▲ **More than 16,000 people infected with the AIDS virus** have taken *VIDEX* (ddI), either through clinical trials or through the company's expanded access program which began in 1989. The expanded access program makes the drug available without charge to patients with AIDS or AIDS-Related Complex for whom the need is critical but who do not qualify for the clinical trials and cannot take AZT.

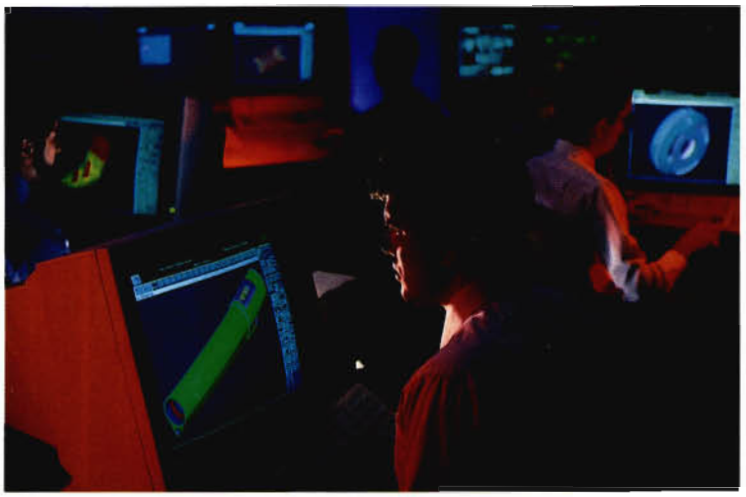
Cefadroxil Victory

● The company won its fight to prevent several generic drug companies from continuing to import and sell products that infringe Bristol-Myers Squibb's patent for crystalline cefadroxil monohydrate, an oral cephalosporin antibiotic marketed as *Duricef* in the U.S. A U.S. District Court and the International Trade Commission concluded that the company's patent is valid and granted the company's request for permanent relief.

▲ ***Sustagen Junior,*** a nutritional supplement for children one to five years old, was introduced during the past year in several markets in Asia. It is patterned after *Sustagen Mighty Drink*, a leading product in Taiwan.

New ACE Inhibitor Launched in the U.K.

● *Staril* (fosinopril) was cleared for marketing in the U.K. in July, 1990, and was launched in February of 1991. It is the company's new once-a-day ACE inhibitor, with a unique metabolic profile which greatly simplifies dosing instructions and compliance in almost all patients regardless of age or renal function. Fosinopril is awaiting FDA approval in the U.S. where it will be marketed as *Monopril*.



▲ **The *Concept*** arthroscopy products business was acquired in June.

▲ **Household Care Products Launched**

New household care products launched during the past year included:

In the U.S.:

—Professional Strength *Drāno*;

—A new line of eleven short handle brushes from Drackett's *O-Cedar* division;

—New potpourri scents for the *Renuzit Freshell* and *RoomMate* and the *Behold* lines;

—*Renuzit* Fragrance Jar.

In Thailand:

—*Windex* Extra Strength.

In the U.K.:

—*Mr. Muscle* Bathroom Cleaner.

In Taiwan:

—Car *Windex*.

In Malaysia:

—*Mr. Muscle* Glass Cleaner.

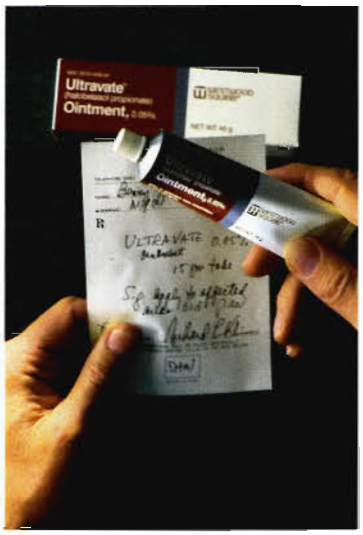
Acquisitions

● Orthoplant GmbH, a manufacturer and marketer of artificial hips and related orthopaedic instrumentation, headquartered in Bremen, Germany, was acquired in January.

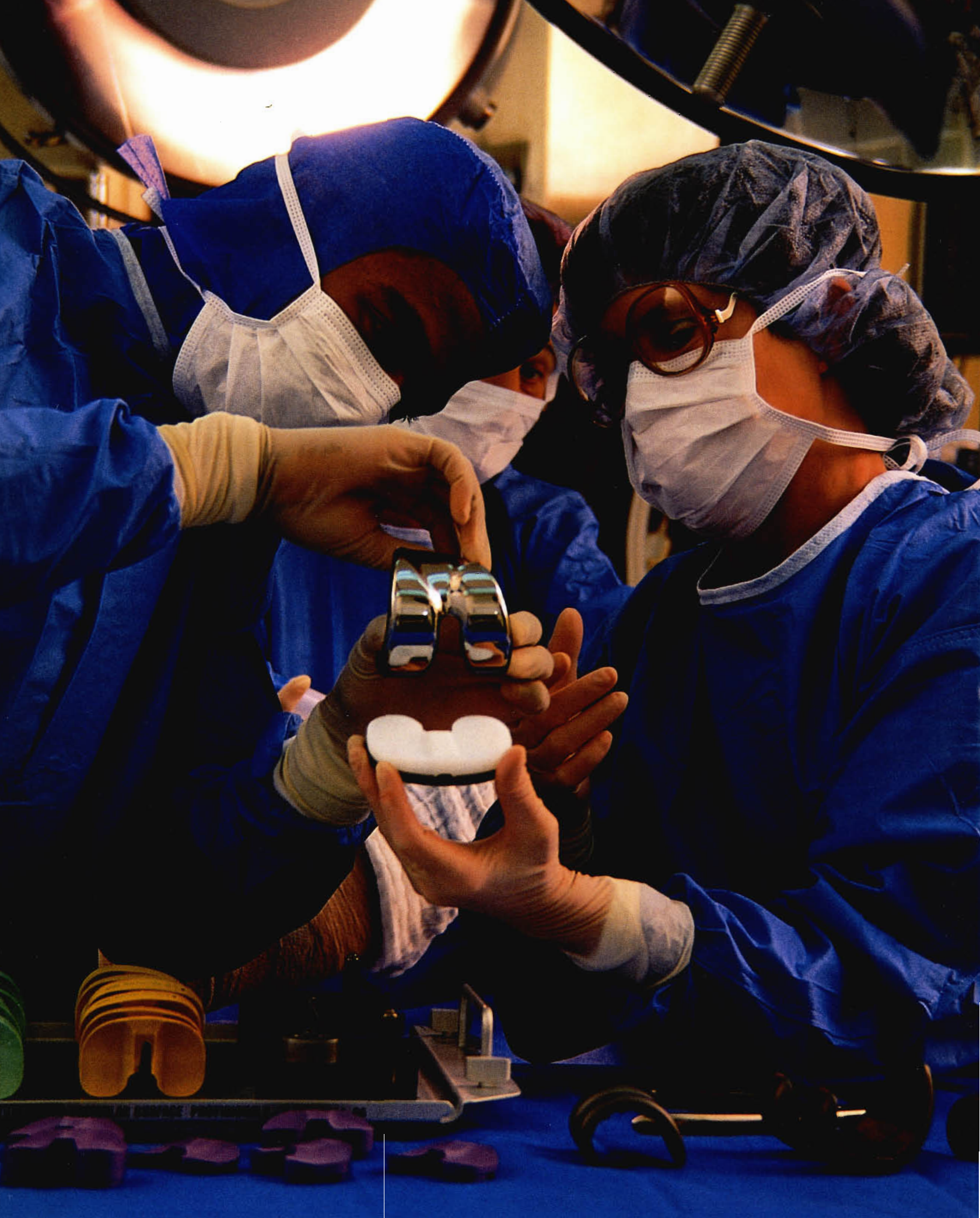
—Joy Corporation, a manufacturer and distributor of salon hair care products in Sydney, Australia, was acquired in February.

—The *Concept* arthroscopy products business was acquired in June.

—S+G Implants GmbH, a manufacturer and marketer of hip and knee implants, headquartered in Lubeck, Germany, was acquired in August from Beiersdorf AG.



▲ ***Ultravate,*** an ultra-high-potency topical steroid, was approved by the FDA in December. It is available in ointment and cream formulations.



The *MG II* Precoat Total Knee System, introduced nationally in March, provides for an enhanced bond between the implant and bone cement used to hold it in place.

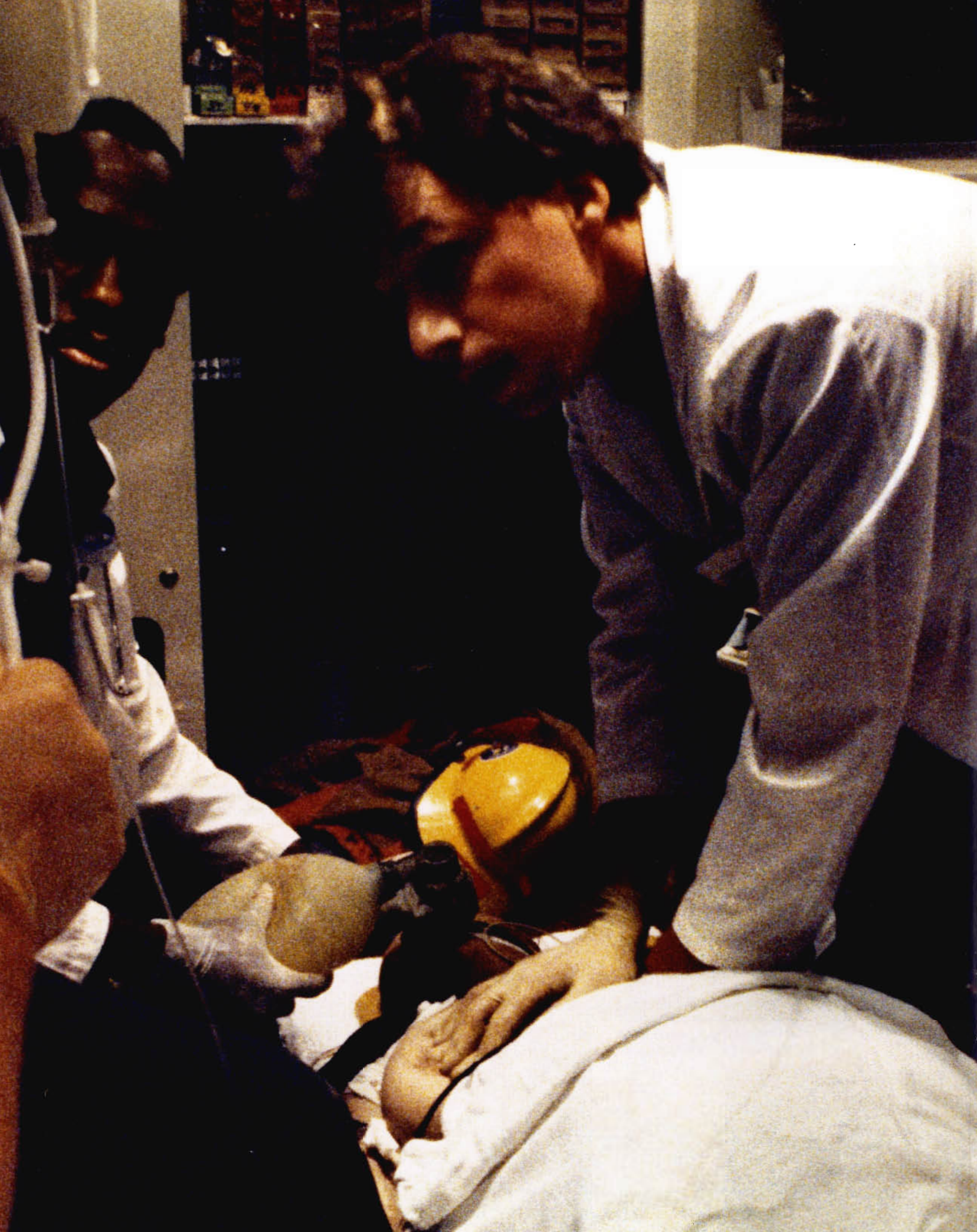
New Orthopaedic and Patient Care Products Introduced

New orthopaedic and patient care products introduced in the U.S. during the past year included:
—*MG II* Precoat Total Knee System;
—Insall/Burstein II Constrained Condylar Knee;
—*Hall Versipower* Dual Powered Orthopaedic Instruments;
—*Concept Slice* Disposable Arthroscopic Blades;
—*MultiPolar* Bipolar Cup for use in hip replacements;
—*Magna Fx* Cannulated Screw Fixation System;
—*Statak* Soft Tissue Attachment Device;
—*Herbert* Cannulated Bone Screw;
—Modular Austin Moore Hip;
—New formulation of *Hemovac Hydrocoat* wound drains and the Snyder *Hemovac* Infection Control System.

New Haircoloring and Hair Care Products Launched

New haircoloring and hair care products launched during the past year included:
In the U.S.:
—*Lock 'n Roll* flexible stylers, designed to work without clips;
—*Kaleidocolors* Powder Lighteners for professional hairdressers;
—A new line of *Condition* Shampoos, Treatments and Styling products.
In Italy:
—*Patterns* Styling Line.
In Taiwan:
—*Finalé* Hairspray.
In New Zealand:
—*Condition*.
In Mexico:
—*Motif* permanent gel colorant.
In Malaysia:
—*Ultress*;
—*Condition* Hot Oil Treatment.
In Thailand:
—*Patterns* Designing Mousse;
—*Clairol Anti-D 2%*, a new therapeutic shampoo formulation for stubborn dandruff;
—*Condition* Hairspray.
In Greece:
—*Condition* Shampoo for permed and color treated hair;
—*Option* Gradual;
—*Loving Care* Mousse. ■

A reformulated *Windex* Extra Strength glass cleaner was introduced in Thailand in March.



Of all the nights in Ronald D. Tegard's life, the one that will stick in his mind forever is the night he died.

8:37 p.m.

Judy Sheridan, a fourth grade teacher, working out in the Seattle Health Club in Seattle, Washington, hears Ronald Tegard thump to the floor.

8:38 p.m.

Dr. Norvin Parr III, a cardiologist and also a club member, checks Mr. Tegard's pulse, finds none, and begins administering CPR with Ms. Sheridan. Her son, Ryan, calls 911.

8:43 p.m.

Captain Mike McIntyre and Engine Company 16 are the first to arrive on the scene. He and his firefighters take over CPR.

8:45 p.m.

Firefighter Ron Calender uses an automatic defibrillator to jump-start Mr. Tegard's stalled heart.

8:46 p.m.

The call for help came in to Medic One at Seattle's Harborview Medical Center. Patty Schultz, a paramedic, arrives on the scene minutes after the firefighters.

Mr. Tegard recalls waking up in the ambulance on the way to Harborview Medical Center. He arrived there within 27 minutes of his heart attack.

Of all the nights in Ronald D. Tegard's life, the one that will stick in his mind forever is the night he died.

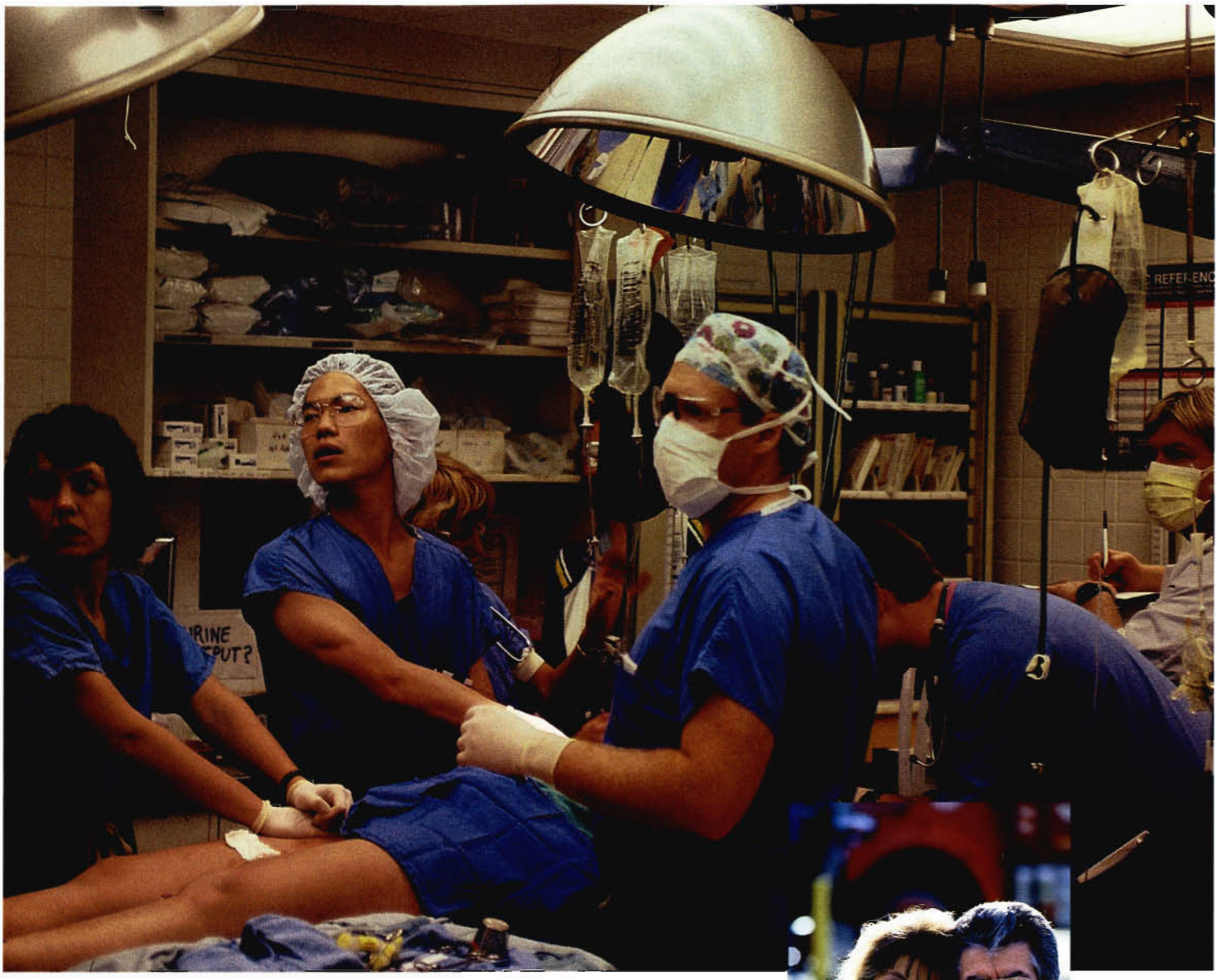
Not that the death itself was particularly memorable. His life history did not flash before his eyes. He did not have an out-of-body experience, nor see spirits in a blinding light, nor have any of the other stock encounters of popular mythology about that great beyond.

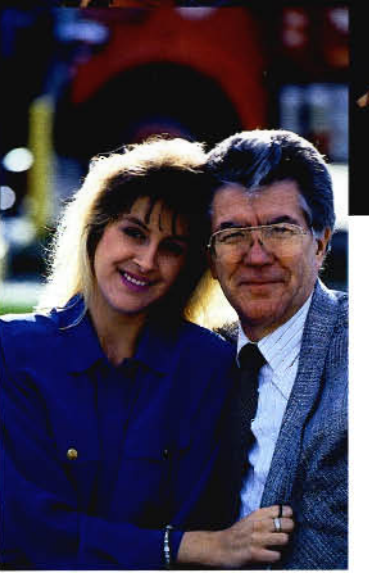
In fact, Mr. Tegard doesn't remember being dead at all. What he recalls are the events just before...and after.

"It was November 10th, 1989," says Mr. Tegard, 56, a staff assistant to the personnel director of the city of Seattle. "I had gone to the health club for my regular Friday night workout. Somebody was using the Nautilus machine that I wanted to use, so I went to the cardiovascular room and did an easy-going 15 minutes on the stair machine to kill time. After that, I wandered over by the water fountain and took a cup of water. I was standing there, sipping water, waiting for this other guy to get done, when suddenly I felt dizzy and started looking for a place to go down. I don't remember hitting the floor."

What had happened to Mr. Tegard is something that befalls many thousands of Americans a year. Without warning, his heart had stopped its regular beating and degenerated into an abnormal rhythm—in his case, an aimless electrical chaos called ventricular fibrillation. His breathing stopped; his pulse vanished; his brain received no blood flow; he turned blue. In a word, he was dead.

"All medical emergencies are urgent, but none are so time-dependent as cardiac arrest. CPR has got to be started within three to five minutes if it's to be effective."





(Above): Doctors and nurses at Harborview Medical Center's emergency room check the vital signs of a patient who has suffered cardiac arrest. (Right): Ronald Tegard, seen here with his daughter Dixi, credits the quick action of the citizens, the firefighters and the paramedics for his survival.

But his story does not end there. Fortunately for Mr. Tegard, he had suffered his cardiac arrest in a city with perhaps the best emergency rescue system in the country. In the vanguard of that system are Seattle's citizens, of whom one in three adults—including Judy Sheridan, a club member who heard Mr. Tegard thump onto the floor—are trained in cardiopulmonary resuscitation (CPR).

"At first, I thought he'd had a seizure," says Mrs. Sheridan, a fourth grade teacher and mother of six. "But another club member who happened to be a doctor checked his pulse and found he didn't have any. So the doctor worked on his chest, and I worked on his mouth, while my 12-year-old son Ryan ran to call 911. It was scary at first. But once I started, everything I had learned in CPR classes came right back to me."

By that time, firefighters from Engine Company 16 were racing to the health club. "Our average response time is three minutes," says Capt. Mike McIntyre, a 22-year veteran who heads the Engine Company, "but this was right on the boundary of our territory, so I'd guess it probably was closer to five minutes that time." On arrival, Capt. McIntyre and his men took over CPR. Then two more firefighters arrived with an automatic defibrillator—a portable version of the shock device that doctors use to jump start a stalled heart. "We put the paddles on him and the machine analyzed his heart rhythm and said to shock him, so we did," says firefighter Ron Calender. "Then it said to shock him again, so we did. After the second jolt, his pulse came back."

"When we got there," adds Capt. McIntyre, "the guy was completely dead. But by the time the paramedics arrived and put in a breathing tube, he was gagging—which is actually a good sign."

Mr. Tegard remembers waking up in the ambulance on the way to Harborview Medical Center, headquarters for Seattle's Medic One rescue team. "I recognized right away where I was because you could hear the siren," he says. "But they had a tube down my throat, so I couldn't make a sound. I was thinking to myself, 'For Christ's sake, let me out of here. I feel okay.' But they kept saying, 'Everything's all right, just relax.'

"The next thing I remember is waking up in the intensive care unit, surrounded by wires and tubes, with my 19-year-old daughter Dixi there. We lost her mother to cancer just a few years ago, and I'm the only family she's got, so she was pretty scared. But once she realized I was basically okay, she was relieved."

Eleven days later, surgeons operated on Mr. Tegard to restore blood flow through two arteries to his heart that—without his realizing it—had become clogged with fatty deposits, depriving the heart muscle of oxygen and precipitating his cardiac arrest. They also implanted a pacemaker-sized device called an automatic implantable defibrillator that monitors his heart and stands ready to deliver a life-saving shock if it ever stops again.

The following week, Mr. Tegard went home. The following month, he and Dixi took the Hawaiian vacation they had been looking forward to. By January, he was back at work full-time. And today, exercising again moderately three times a week, Mr. Tegard feels nearly as fit as he did before dying. "In some ways, it was just an incident that happened, and that's that," he says. "You try to forget it. But I cannot stress enough how important it was that those two people knew CPR and that the fire department and Medic One came so quickly. That's what really saved me."

His doctors heartily concur. "All medical emergencies are urgent," says Dr. Leonard A. Cobb of Harborview Medical Center and the University of Washington, the founder of Medic One, "but none are so time-dependent as cardiac arrest. CPR has got to be started within three to five minutes if it's to be effective. And CPR is just a holding action. For patients in ventricular fibrillation like Mr. Tegard, you've got to follow with electric shock as soon as possible or you risk irreversible brain damage. The longer the delay, the worse the outcome."

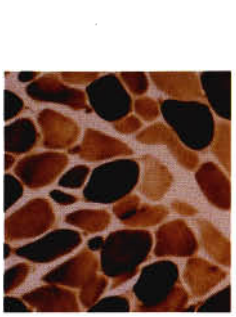
A Disease on the Run

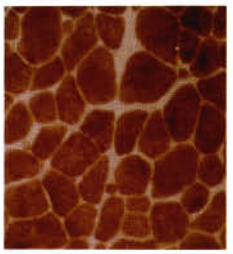
Cardiovascular illness is slowly becoming a disease on the run. The pandemic of coronary heart disease—in which the heart muscle is damaged due to insufficient blood flow through the coronary arteries—dominated medicine in the developed world during the middle of this century. But now, it is on the wane, with death rates from coronary heart disease in the U.S. down about 50 percent from their mid-1960s peak. Why? A combination of improved treatment for conditions like high blood pressure and high cholesterol and the simple fact that Americans are living healthier lives—smoking less, exercising more and eating less fat.

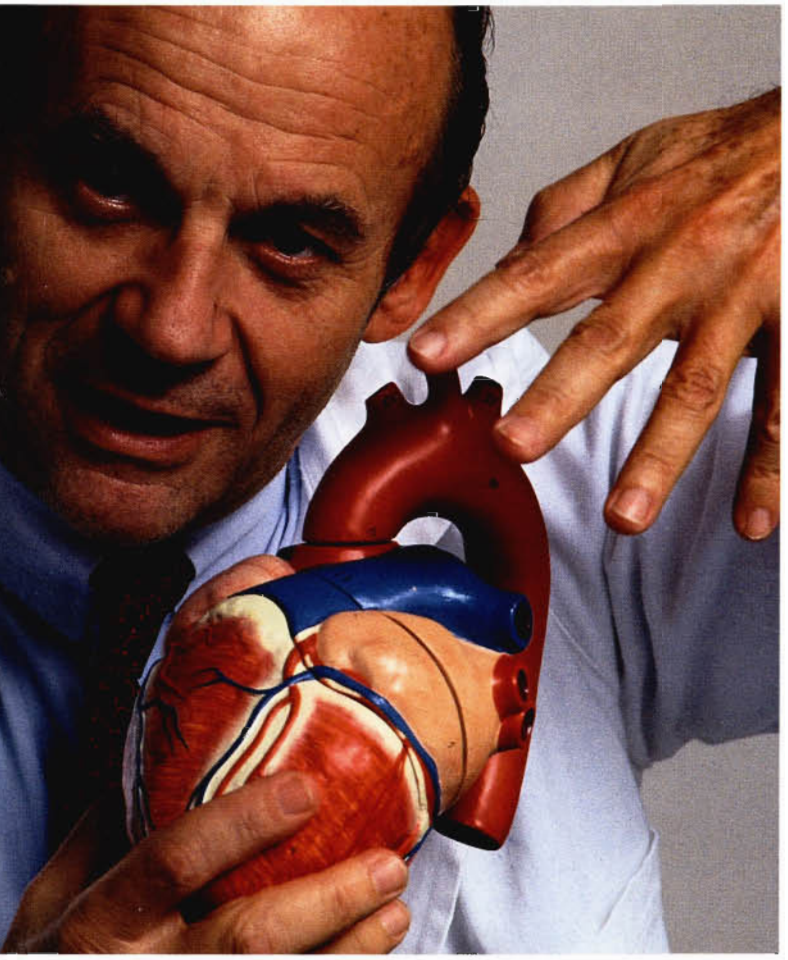
The Seattle program, and others like it across the country, are part of a general movement toward earlier, more aggressive treatment for heart disease that is taking place worldwide. Surgeons have devised better ways to repair damaged hearts while cardiologists treat a growing number of patients with non-surgical procedures. Pharmaceutical research scientists have discovered safer, more powerful drugs. Epidemiologists are pinpointing new environmental factors that contribute to heart disease. Geneticists are identifying many of the genes that determine an individual's susceptibility. And biologists are unraveling the complex web of chemical and biological signals by which the circulatory system operates, holding the promise of even more sophisticated treatments to come.

"In the last 10 years there has been a literal explosion in our knowledge," says Dr. Russell Ross, a University of Washington pathologist who is in the forefront of blood vessel research. "Advances in cell and molecular biology have given us the tools to ask questions that we couldn't even ask before, and get reasonable answers."

Yet it is too soon for celebration. Heart disease in its many forms afflicts about one in four Americans, when the estimated 62 million people with high blood pressure







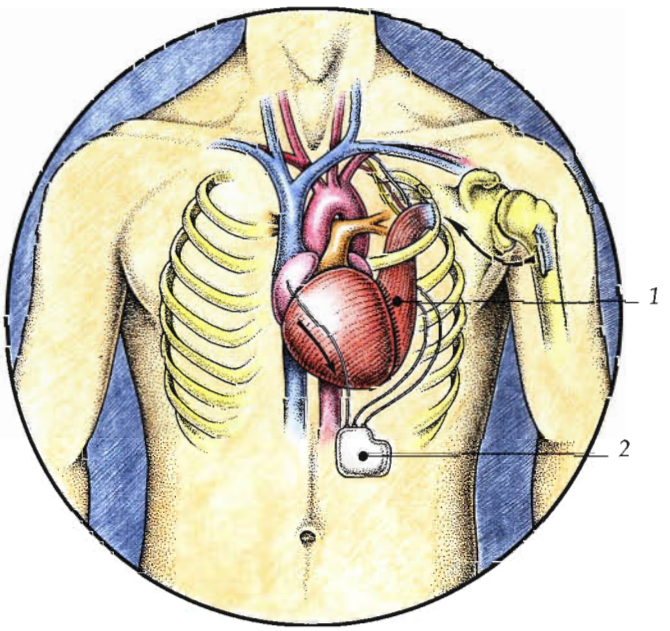
(Left): This French woman, pictured here with her husband, underwent the first dynamic cardiomyoplasty in 1985 when she was dying from her failing heart. (Above): Dr. Alain Carpentier developed a technique to wrap the pumping chambers of a failed heart with a portion of muscle from the back, training the cells in the transplant to beat by stimulating them electrically. (Top): Transplanted skeletal muscle, dominated by fast twitch fibers (stained in black on left), eventually change almost entirely to the slow twitch fibers (stained in brown on right) that are more resistant to fatigue, after several months of electrical stimulation.

are included. It is still the leading killer in the United States and Europe—responsible, for example, for about 45 percent of all U.S. deaths, a toll of nearly a million lives each year, or one every 32 seconds. And it is a leading cause of death around the globe, responsible for some 12,000,000 fatalities annually. The price tag for these illnesses is staggering. In the United States alone, the cost for doctors, nurses, hospitals, nursing homes, medications and lost productivity is estimated by the American Heart Association at $101.3 billion a year. That is why cardiovascular researchers remain relentless in their pursuit of new ways to fight the disease.

Rebuilding the Heart

Sometimes, an idea that seems perfectly obvious in retrospect has to wait until the right time to be discovered. For example, it was not until about 108 years after the first use of general anesthesia—which opened the door to so many other kinds of surgery—that Dr. John Gibbon performed the first successful open heart operation. Why did it take so long? Because anesthesia wasn't enough. Successful heart surgery also had to await advances in diagnostics, anticoagulation and, most importantly, the creation of the heart-lung machine that maintains blood flow while the heart is stilled.

Muscular Assist for a Failing Heart



This drawing shows how Dr. Alain Carpentier and his colleagues help patients who need a heart transplant but have no donor heart available. 1. The surgeons detach a flap of back muscle and stitch it around the pumping chambers of the heart. 2. After gradual training by an implanted, battery-powered electronic stimulator, the transplanted muscle eventually can beat as rapidly as the normal heart muscle without getting tired.

Today, U.S. surgeons do about 650,000 open heart operations a year—including more than 350,000 coronary bypass operations aimed at restoring blood flow to the heart itself. In this operation, doctors borrow snippets of vein from the leg or vessels from elsewhere in the body and stitch them to the coronary arteries that nourish the heart. The result is to route blood around and past the obstruction caused by atherosclerotic plaque. In a variation of the same procedure, they augment blood flow to the heart by redirecting an internal mammary artery, a blood vessel that usually supplies the muscles of the chest.

While the bypass operation can restore blood flow and, for many patients, improve survival and the quality of life, surgeons until recently remained frustrated in a more ambitious dream—that of repairing a failing heart. During the first half of this century, the French surgeon René Leriche did animal experiments in which he would create a hole in the heart muscle—analogous to the dead tissue that is left after a heart attack—and then fill it with a plug of ordinary skeletal muscle. But the experiments failed because the implanted tissue lacked a blood supply and did not survive.

More recently, French and American surgeons tried transplanting flaps of muscle from the chest with their blood supplies intact. They even stimulated the transplanted flap electrically, to make it contract. But they ran square into a basic biological obstacle. As Dr. Alain Carpentier of the University of Paris explains: "The heart being a pump that has to work all the time, it is composed of muscle that is not prone to fatigue. The skeletal muscles are much stronger and contract faster, but if they work without rest, they soon tire. So after several hours or days, the transplanted muscle stopped contracting—even with stimulation—and the patient did not get long-term support.

"I got the idea that, if the operation fails, maybe it is because they are trying to stimulate the transplant at the same rate as the heart from the very beginning," says Dr. Carpentier, chairman of cardiac surgery at Broussais Hospital and inventor of an important surgical heart-valve repair technique. "So I thought, why don't we 'train' the transplanted muscle instead by raising the stimulation gradually."

Thus was born an extraordinary operation called dynamic cardiomyoplasty that can preserve the lives of patients who would die without a heart transplant but for whom no donor heart is yet available. To help these patients survive the long wait, Dr. Carpentier and colleagues, including engineer Pierre Grandjean and Dr. Juan-Carlos Chachques, take a flap of the back's latissimus dorsi muscle and wrap it like a blanket around the main pumping chambers of a failing heart. At the same time, they implant an electronic device not much larger than a pacemaker that senses the heart rhythm and stimulates the muscle transplant to contract.

"We control the stimulator from outside the body using telemetry," says Dr. Carpentier, "so that, at the beginning, the muscle contracts only on one heartbeat out of every three. Then we gradually raise the pace of contractions and increase the electrical frequency of stimulation. After six weeks, the muscle beats at the same rate as the heart and with full force. We have done about 35 patients altogether, although we are now doing operations up to once a week, and some of our earliest patients—who would otherwise have died—remain alive after five years."

Even more importantly, after several years the microscopic composition of the transplanted muscle—which started out being dominated by "fast twitch" fibers characteristic of skeletal muscles—changed to become composed almost entirely of "slow twitch" fibers that are much more resistant to fatigue. "This biological transformation forms the basis of this new surgical operation," says Dr. Carpentier.

Non-Surgical Surgery

They can be found at any large scientific meeting: the poster sessions, usually held in some cavernous hotel ballroom, where hundreds of scientists put up posters describing their work and hundreds more stroll around to observe.

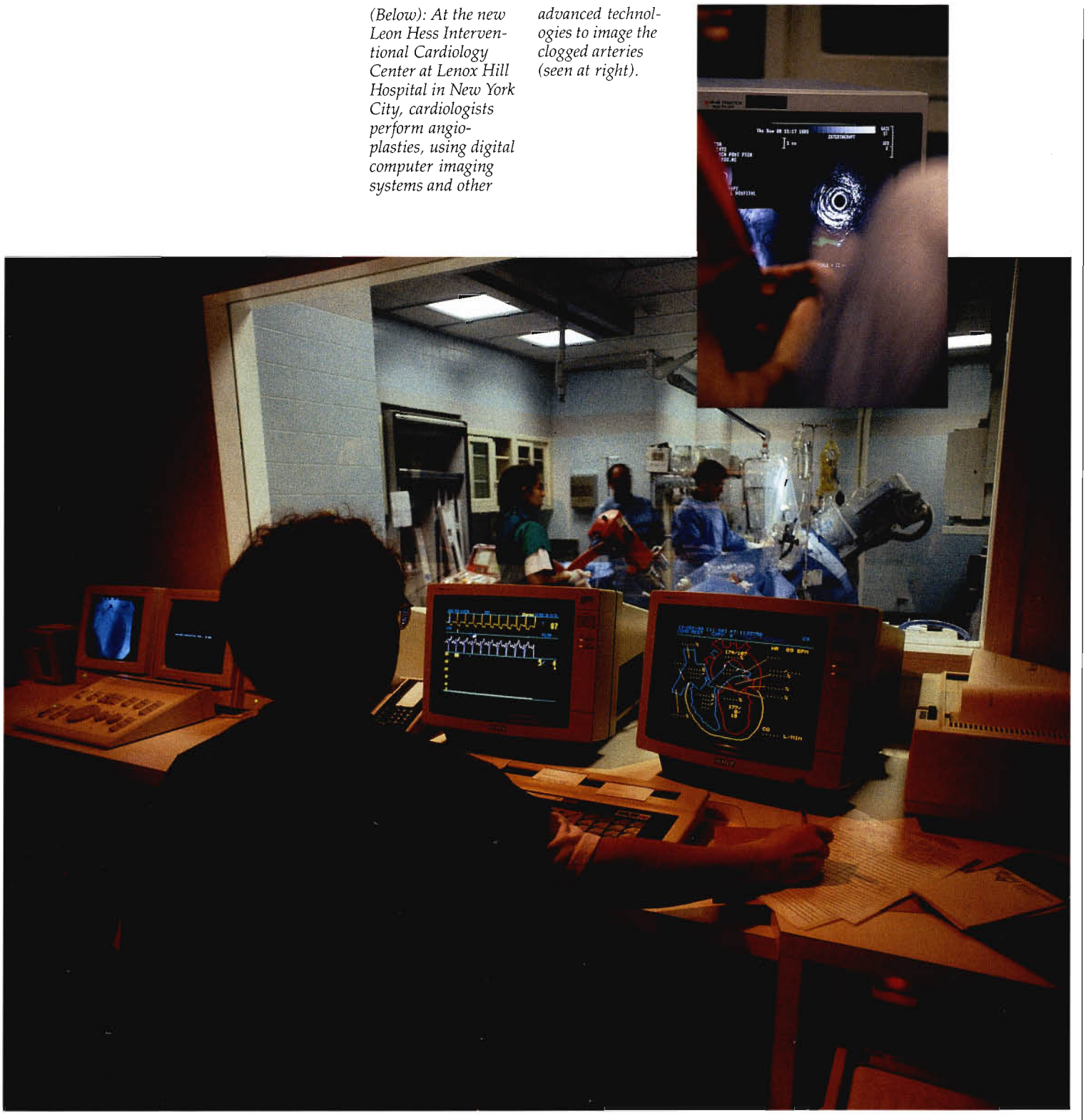
These free-for-all show-and-tells serve an important purpose. They help disseminate new information and often spark important collaborations, as Dr. Spencer B. King, III of Emory University in Atlanta can attest. "In 1976," says Dr. King, "I was showing some work at a poster session of an American Heart Association meeting in Miami when a friend came by and said, 'Hey, you've got to see this poster in the next row.' So I went over and found a European cardiologist named Andreas Gruentzig who was presenting some animal work. He had tied a silk ligature around an artery to narrow it. Then he put in a flexible catheter [a hollow tube] that had a balloon on its tip, and inflated the balloon to break the thread and open the artery.

"His point was to show that this was technically feasible. But he wanted to do the same thing to open blocked arteries in patients. Frankly," laughs Dr. King, "it looked very bizarre and I wondered whether the guy had all his marbles. I was less than blown away, you might say."

But Dr. King and cardiologists everywhere were very impressed indeed the following year, when Dr. Gruentzig successfully performed that very procedure on a heart patient. Dr. King and his colleagues were soon on their way to Zurich to witness the feat first hand. That led to a working friendship. And that led, in 1980, to Dr. Gruentzig leaving Switzerland and joining the staff at Emory, where he stayed until his death five years later.

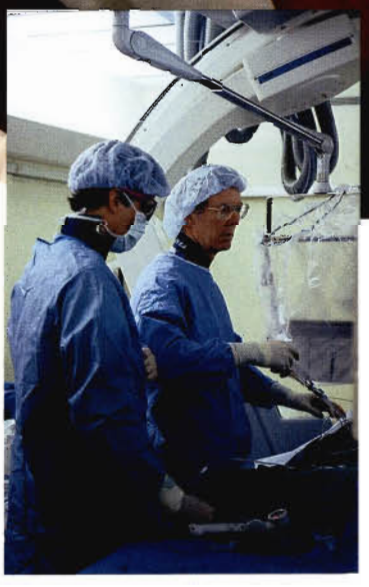
This year, the operation that Dr. Gruentzig pioneered—known formally as percutaneous transluminal coronary angioplasty or PTCA—will be repeated well over 200,000 times in the U.S.—remarkable for a procedure a little over a dozen years old. Its popularity is easy to explain. Using balloon-tipped catheters that are inserted through an

(Below): At the new Leon Hess Interventional Cardiology Center at Lenox Hill Hospital in New York City, cardiologists perform angioplasties, using digital computer imaging systems and other advanced technologies to image the clogged arteries (seen at right).



"This year, coronary angioplasty will be repeated well over 200,000 times in the U.S.—remarkable for a procedure a little over a dozen years old."

"Prior to this operation, all we could offer patients was a cracked chest. Now we have an alternative."



(Above): Three-month-old Rodney Minor, Jr., pictured with his father, underwent a balloon angioplasty to correct a congenital deformity in his artery. (Right): Dr. Spencer King says that a number of new technologies are being developed that could make the use of catheters to open clogged blood vessels even more effective.

artery in the leg, cardiologists are able to open clogged blood vessels that would otherwise require surgery—and at a much lower cost per procedure. As Dr. Gruentzig himself once put it, "Prior to this operation, all we could offer patients was a cracked chest. Now we have an alternative."

"We recently looked back at some of the early patients we did at Emory," says Dr. King, director of the Andreas Gruentzig Cardiovascular Center. "Our goal had been to solve their problem—which was usually angina [chest pain resulting from an inadequate blood supply]—without them having a heart attack or needing to go for surgery. And 80 percent of the time, we succeeded—proving that you can get good long-term results."

One important problem persists, however. In about 30 percent of patients, the vessels that have been opened by angioplasty close again within the next three months or so. Patients then require either a second angioplasty or, in some cases, coronary bypass surgery.

Cardiologists are experimenting with implantable devices called stents that can hold the vessels open. "Stents are extremely useful for large vessels and those in danger of imminent collapse," says Dr. Roger Hall of University Hospital in Cardiff, Wales. "But you are fighting one of the body's basic repair mechanisms. When you expand the artery with the balloon you are causing injury to the blood vessel and it is trying to heal itself. That's why I believe the solution to this problem will eventually be a biological one, not a mechanical one like the stent."

While scientists have not yet solved the problem, they are pursuing several good leads. For example, one of the first things that happens after angioplasty is that clot-promoting blood components called platelets adhere to the injured vessel wall. Platelets make a growth factor—known simply as platelet-derived growth factor, or PDGF—that can also be made by immune cells and cells of the blood vessel lining. Scientists think PDGF and other growth factors may be responsible when excessive re-growth clogs the artery once again.

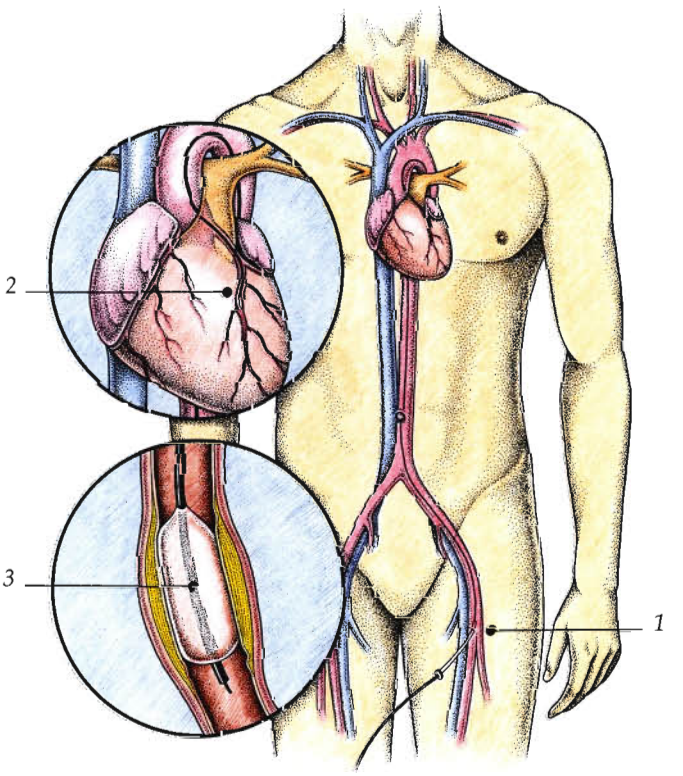
At the University of California at San Francisco, Dr. L.T. "Rusty" Williams of the Howard Hughes Medical Institute and his colleagues have managed to clone the receptor for PDGF. "Our goal is to block PDGF function," says Dr. Williams. "We might, for example, make a soluble form of the PDGF receptor that could be injected into the bloodstream like a drug. It would sop up the PDGF before it could trigger excessive growth."

Across the continent at the Massachusetts Institute of Technology, genetic engineers have worked out a system that might deliver such a drug. Dr. Richard C. Mulligan and his co-workers at the Whitehead Institute for Biomedical Research demonstrated that genes could be efficiently transplanted into endothelial cells, the cells that normally line blood vessels. The genetically modified cells could either be seeded onto artificial blood vessels, and then implanted into animals, or directly seeded onto natural arterial segments of living animals. In both cases, the inserted gene was expressed.

"In principle," says Dr. Mulligan, "such cells might provide a novel means of delivering a wide variety of biologically active products to local regions of the vasculature. While this approach is still clearly in the very early experimental stages, it represents a potentially powerful new approach to the treatment of cardiovascular disease."

In the meantime, Dr. King and others point out, the majority of patients do fine after angioplasty. And what about that poster of Dr. Gruentzig's that Dr. King first saw in Miami years ago? "It's hanging on my wall," he says.

How Balloon Angioplasty Works



Doctors use a non-surgical technique called balloon angioplasty to clear a partially blocked coronary artery. 1. A cardiologist inserts a catheter (a flexible hollow tube) into an artery in the leg. 2. He guides it up through the blood vessels to the heart using X-ray images to monitor its progress. He then passes a second, smaller tube with a sausage-shaped balloon at its tip through the catheter. 3. Positioning the balloon across the narrowed portion of the artery, he inflates it to open the blood vessel.

Innocent Bystanders

It is no accident that surgeons and cardiologists are becoming intensely interested in the basic biology of blood vessels. As Dr. Victor J. Dzau, William C. Irwin Professor of Cardiology and chief of Stanford University's Division of Cardiovascular Medicine, explains, "There is now a growing recognition that most cardiovascular diseases—including heart attacks, heart failure, stroke and kidney disease—are really *blood vessel* diseases. Risk factors like hypertension, diabetes and smoking do damage to the blood vessels, and that results secondarily in harm to the heart, brain or kidney. But these end organs are really just innocent bystanders."

This focus has led to several insights, one of which is that although death from heart disease can occur in moments, the events that lead up to it may take a lifetime. Atherosclerosis, the condition in which harmful plaque clogs the arteries, provides a good example. "The first stage in atherosclerosis is the appearance of a so-called fatty streak," says the University of Washington's Dr. Russell Ross. "This is composed of fat-rich cells that look to the naked eye like a pale or yellowish streak. Fatty streaks appear in some children as early as age two or three, probably because of our society's fat-rich diet.

"As the person grows, and the original insult—be it factors such as diet, cigarette smoking or whatever—continues, the fatty streak evolves through a continuous series of changes. First, white blood cells adhere to the endothelial cells that line the artery. Some of the white cells enter the lining and undergo changes characteristic of inflammation. Meanwhile, the endothelial cells may be stimulated to secrete growth-regulatory factors, as may the white blood cells, and smooth muscle cells that lie underneath the endothelium start to proliferate.

"This process continues and eventually, in the advanced lesion, you get a fibrotic mixture of lymphocytes, macrophages [both types of immune cells] and smooth muscle cells. In the U.S., because of our diet, these latter two cells are often filled with fat. But the same thing can happen without the fat in response to other risk factors, like hypertension or smoking. The common end point is a proliferative fibrotic lesion."

The notion that atherosclerosis represents a blood vessel's futile effort to heal itself was first advanced by Dr. Ross and colleagues in the 1970s. They called it the "response to injury" hypothesis. "Essentially," he says, "the advanced lesion is a case of healing run amuck. In theory, if the person became a vegetarian or gave up smoking, the lesion might stop progressing. It's conceivable that lesions appear and disappear all the time and you never know it. But my suspicion is that you reach a critical point where the lesion compromises so much of the space within the artery that the person can be subject to heart attacks, strokes or gangrene in an extremity."

These insights into the natural history of heart disease have been accompanied by a revolution in the drugs used to treat it. Research into the details of fat metabolism, for example, led to the discovery of a new class of agents that are the most potent yet in lowering cholesterol. They work by inhibiting an enzyme called HMG Co-A reductase, which governs the rate at which the body makes cholesterol.

"We know that people can reduce their cholesterol by modifying what they eat," says Dr. Allan M. Lefer, chairman of physiology at the Jefferson Medical College of Thomas Jefferson University in Philadelphia. "But we also know that the American public's habits cannot be changed overnight, so we need help. And these HMG Co-A reductase inhibitors can lower the risk of coronary events very significantly."

The drugs work on cholesterol in two ways. First, by blocking the HMG Co-A reductase enzyme, they prevent the liver—the body's main cholesterol-synthesizing organ—from producing so much of the pearly, fat-like substance. That, in turn, causes the liver to remove more circulating cholesterol from the blood. Researchers now are looking for even better ways to achieve the same effect. One approach might be to inhibit other enzymes involved in cholesterol synthesis. An alternate method could be to leave synthesis alone and find a drug that would cause the liver to snag more cholesterol from the blood.

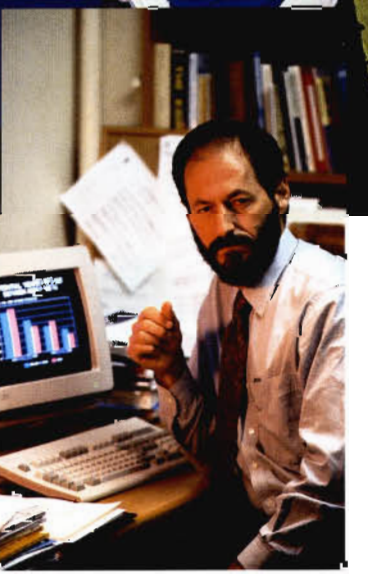
Another important change has come with the new emphasis on controlling blood pressure. It has been known for years that severe high blood pressure, or hypertension, accelerates atherosclerosis and can damage the blood vessels, heart, brain and kidneys. But in a recent study of nearly 1,000 Tecumseh, Michigan, residents, Dr. Stevo Julius and his colleagues at the University of Michigan Medical Center discovered that even minimal hypertension can be damaging.

"We found that in people with borderline hypertension—meaning a blood pressure of around 140 over 90—there was evidence of blood vessel thickening," he says. "When the vessel is thicker, it offers more resistance to the heart, so the heart works harder, setting in motion the vicious circle that can lead to heart disease." In his own practice, Dr. Julius first recommends that such patients exercise and lose weight to control their blood pressure. If that fails, he may prescribe antihypertensive drugs.

In control of hypertension, too, there have been significant changes in drug therapy, especially during the last decade with the introduction of so-called angiotensin converting enzyme (ACE) inhibitors. These drugs block the enzyme that otherwise can liberate a powerful pressure-raising substance (angiotensin II).

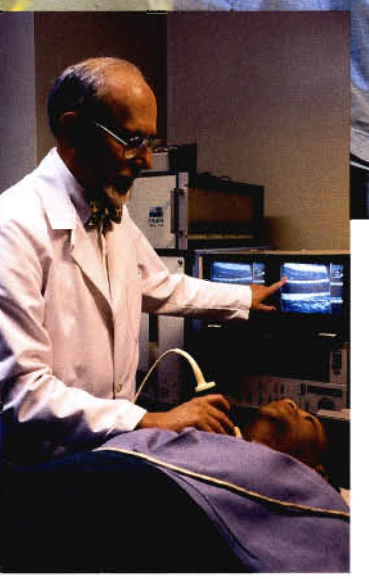
Some ACE inhibitors, like some other drugs, may have a further potential advantage in that they increase the body's responsiveness to insulin, a hormone that controls the level of sugar in the blood. That fact may be of particular importance to diabetics, who frequently suffer from insulin resistance and are terribly prone to heart or blood vessel disease: about four-fifths of them die of it. Insulin resistance also may be an important factor in many hyper-

"Heart disease in its many forms afflicts about one in four Americans, when the estimated 62 million people with high blood pressure are included."



(Top): Graduates, ages 41 to 84, of the Cardiac Rehabilitation Program, a course for heart attack survivors at Massachusetts General Hospital in Boston. (Right): Dr. Michael Gideon Marmot has been conducting studies on several population groups, including Indians and Pakistanis in East London, at the University College and Middlesex School of Medicine, linking heart disease risk to elevated levels of blood insulin.

"When I was in school, we were brought up to think of blood vessels as sort of inanimate rubber tubes. That will never be the case any more."



(Above): Dr. Paul Vanhoutte, director of the Center for Experimental Therapeutics at Baylor College of Medicine in Houston, Texas, looks at isolated blood vessel tissue in seeking new clues to understanding the role of endothelial cells in producing the relaxing factors which keep blood vessels open and blood flowing. (Right): Dr. David H. Blankenhorn's studies indicate that aggressive treatment of patients with blocked coronary arteries, using exercise, medications and diet, could lead to a reduction in atherosclerotic plaque.

tensives without diabetes in whom other types of antihypertensive therapy may worsen their insulin-resistant state.

"Recently, a number of studies—including some we did on Indians and Pakistanis in East London, who are more likely than their British neighbors to die of heart disease—have linked heart risk to high blood insulin levels," says Dr. Michael Gideon Marmot, head of the Department of Community Medicine at Middlesex School of Medicine in London. "That squares well with our understanding of so-called maturity-onset diabetes. In contrast to juvenile-onset diabetes, which results from a lack of insulin, the maturity-onset disease often results from a state of resistance to the hormone. The tissues stop responding to insulin, so the body makes more of it—leading to increased levels of insulin in the blood." Scientists still aren't sure how that provokes heart disease. But one possibility is that since insulin also acts as a growth factor, it contributes to the thickening of blood vessel walls, a problem in high blood pressure and atherosclerosis.

A third pharmacological revolution has come with the use of clot-busting drugs for people who suffer a heart attack. This innovation flowed from the discovery that, in most heart attacks, the event that actually seals off blood flow to the heart is a sudden clot in a plaque-narrowed vessel. "We used to think clots were not very important in causing heart attacks," says Dr. Desmond G. Julian, a cardiologist and Medical Director of the British Heart Foundation in London. "The reason was that post mortems on victims often failed to find them. But we now know that, once a person dies, his blood fills with powerful anti-clotting substances that melt the clots away." Today, doctors routinely give clot-dissolving drugs like tissue-type plasminogen activator or streptokinase to people who are having a heart attack in order to clear any clots and restore blood flow.

One stubborn mystery, though, is why some people suffer clots while others don't. "We're all running around with atherosclerotic plaque," says University Hospital's Dr. Roger Hall. "You've got plaque. I've got plaque. But for some of us, this plaque causes a clot, and for others it doesn't, and we're only now beginning to learn why."

Doctors have known for years that clots are sometimes caused when the protective inner lining of the artery tears, exposing the blood to clot-promoting substances underneath. But recent research on both sides of the Atlantic suggests there may be a pattern to such fatal events. By studying autopsy tissue, Dr. Michael Davies of St. George's Hospital Medical School in London found that most tears occur where there is a soft pool of fat hidden under the plaque on one side of a blood vessel.

"The cap over this fat is often much stiffer than the surrounding tissue, whereas the fat underneath is much softer—about the consistency of soft cheese," says Dr. Peter Damian Richardson of Brown University in Providence, Rhode Island, one of Dr. Davies' collaborators.

Dr. Richardson's computer models show that this combination tends to concentrate stress in the blood vessel at the junction between hard cap and surrounding tissue—exactly where most plaques tear. That suggests a novel approach to therapy: drugs might be invented that either modify the hardness of the plaque cap or actually make the semi-liquid fat a little stiffer, so that it could bear more of the load.

Yin Versus Yang

The endothelium, the delicate lining of blood vessels, is only a single cell thick. Yet through it must pass everything that moves between the bloodstream and the tissues, including oxygen, nutrients, waste, hormones and even entire cells. And for that reason it has become a critical target in understanding the origins of atherosclerosis.

"There is a yin-yang quality to the endothelium," observes Dr. Michael A. Gimbrone Jr., a Harvard Medical School pathologist who directs the Vascular Research Division at Boston's Brigham and Women's Hospital. Though scientists once thought of the endothelium as little more than a passive conduit, they now know "it is the pivotal point of dynamic pro and con forces that control a variety of physiological functions, including blood pressure, vasospasm, clotting and the integration of hormonal messages," according to Dr. Gimbrone.

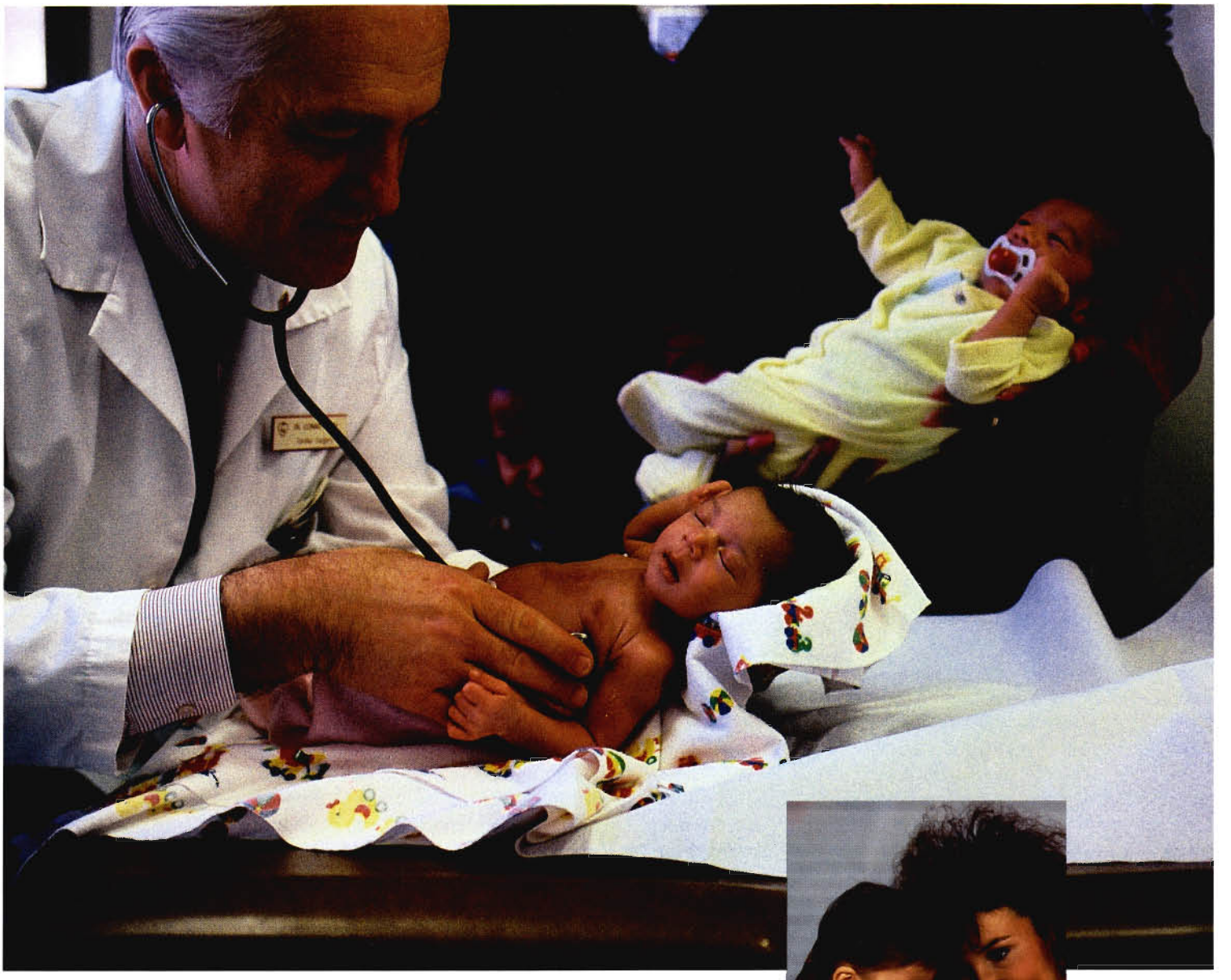
Dr. Gimbrone's own laboratory has recently revealed one aspect of this yin-yang character. The yin appeared when he and his colleagues discovered that endothelial cells could display on their surface a particular type of protein—they call it an endothelial-leukocyte adhesion molecule—that snags passing white blood cells. "That was exciting because it showed the endothelium could be a positive player in selecting which cells stick during the inflammatory process that leads to plaque formation," says Dr. Gimbrone.

The yang soon followed. By hunting carefully in the wash fluid that would normally have been discarded after their experiments, the scientists found an antithetical substance that inhibits white blood cell sticking. "This was one time we were glad we didn't literally throw the baby out with the bath water," says Dr. Gimbrone. They and others are now looking for drugs that could stop the cells from sticking where they shouldn't.

The endothelium's yin-yang character popped up again in research concerning what causes blood vessels to expand and contract. The story began around 1980, with the discovery that the endothelium makes a factor that causes adjacent smooth muscle cells to relax, thus enlarging the vessel. Scientists later identified this endothelium-derived relaxing factor (EDRF) as nitric oxide.

Meanwhile, the opposite of EDRF turned up in research halfway around the world at Tsukuba, Japan. Dr. Masashi Yanagisawa and his co-workers in the Institute of Basic Medical Sciences at Tsukuba University had been fascinated by studies suggesting that the endothelium could

"We were devastated. But for us there was no alternative—we just couldn't sit there and let him die."



(Above): Dr. Leonard Bailey, head of the Loma Linda infant heart transplant program, reviews transplant procedures for two newborns. (Right): Nicholas DeWitt, here with his parents, Antonella and Brad, received a new heart at the Loma Linda transplant center just ten days after he was born.

make a contrary substance that constricted vessels. "We set up a very large-scale endothelial cell culture operation in April 1987, and by August we had purified a batch of the factor, which we call endothelin," Dr. Yanagisawa says. "It may be the most powerful blood vessel-constricting substance known. We published our first paper in [the British science magazine] Nature in 1988. This aroused so much interest that there have been over 700 publications on endothelin since then, an average of almost one per day!"

Dr. Yanagisawa has recently cloned the gene for the receptor through which endothelin acts upon cells, which could open the door to new drugs for treating heart attacks, kidney disease and blood pressure.

Scientists now think a disruption in the balance between such constricting and relaxing factors may be central to many cardiovascular illnesses. "This is one of the most striking things that has emerged from our research," says Dr. Paul M. Vanhoutte, director of the Center for Experimental Therapeutics at Baylor College of Medicine in Houston. "In almost every experimental model of blood vessel disease, endothelial cells are less capable of producing the 'good guys'—the relaxing factors that keep the tubes open and the blood flowing—while they are either unchanged or actually enhanced in their ability to produce the 'bad guys' that constrict the tubes and keep them closed."

Adds Dr. Peter Libby, director of the Vascular Medicine and Atherosclerosis Unit at Brigham and Women's Hospital, "When I was in school, we were brought up to think of blood vessels as sort of inanimate rubber tubes. That will never be the case any more."

The Littlest Victims

The grim meeting took place just two days after little Nicholas DeWitt was born. The eight-pound, six-ounce hazel-eyed boy had seemed healthy enough when he was delivered at the hospital in Edmonton, Alberta, Canada. But a day or two later, a nurse noticed that his legs took on a bluish cast during a crying fit. After looking at his internal organs using ultrasound, doctors transferred him to the University of Alberta. And it was there, on December 13, 1989, that an anxious Antonella and Brad DeWitt confronted three somber-faced physicians.

Nicholas, the doctors told them, was among the 25,000 babies born each year with a congenital heart malformation. In his case, the problem was hypoplastic left-heart syndrome, in which the main pumping chamber fails to develop. Such babies always die without treatment.

"We were devastated," remembers Antonella, 28, a secretary at the university. "But for us there was no alternative—we just couldn't sit there and let him die. And even though they told us that the condition was usually 100 percent fatal, I knew in my heart that Nicholas wasn't going to die. Call it mother's intuition, shock, disbelief, whatever, I had a good feeling about him. I knew he would be all right."

One reason for her confidence was that the DeWitts knew about the infant heart transplant program at Loma Linda University Medical Center outside Los Angeles. Two babies from the Edmonton area had received new hearts there earlier, and the operations had been covered by Canadian newspapers and television stations.

Indeed, the Loma Linda program, the first of its kind when it began just over six years ago, has now spawned imitators in a number of major U.S. medical centers—thanks to an amazing discovery about transplants and babies. "You have to remember that newborn infants have just come out of a situation—the womb—where their immune systems have been held in check," says Dr. Leonard L. Bailey, head of the Loma Linda team. "Otherwise the baby would have rejected the mother, or vice versa.

"What we do is capitalize on that state of immune suppression, some of which is still hanging around after birth. If you transplant a baby within the first 30 days of life, it is much less likely to reject the transplanted organ than is an adult or older child. So there is a window of opportunity there. The sooner you do it, the better."

On December 20, word came that a donor organ had been found. The tiny patient, by then being sustained only by an incubator and drugs, was rushed to Los Angeles in a Lear jet that night. His parents followed the next day and, by the time they arrived, the operation was over and had been a success.

"There are 2,500 to 3,000 babies born in the United States every year who potentially could benefit from heart transplants, if we could find enough donors. Too many of them die for no good reason," says Dr. Bailey. "We already know that our transplant babies become perfectly healthy children. The oldest have recently celebrated their fifth birthdays. I feel confident they will grow up to have families of their own, and I dearly hope to see that before I am dead and gone."

The DeWitts won't have to wait that long for their reward. "Our high point is just seeing him now," says Brad of his 13-month-old, 23-pound son. "I know every parent is proud of his child. But when I take Nicholas out to the park this afternoon, probably three people will come up to me and say how beautiful he is. Strangers always stop us, and if we get to talking and they find out he had a transplant, they don't believe it. They say, 'But he looks so healthy.' And the nice part is, he is."

The Case of the Disappearing Plaque

Even while the guns still thundered at the front during World War I, the Allied blockade of Germany drew a noose around the civilians back home. Margarine replaced butter; rye replaced wheat in flour, then potatoes replaced the rye. Turnips were pressed into service when the potato crop failed in the winter of 1916. The German soldiers home from the trenches would find "vegetable butter" on the dinner table made from beets, carrots and seasoning; salad oils squeezed from plant mucilage; and an egg substitute concocted of maize and potato meal.

"During those war years," says Dr. David H. Blankenhorn, director of the Atherosclerosis Research Institute at the University of Southern California School of Medicine, "the German doctors who did autopsies on civilians noticed that the number of atheromas [the yellowish plaques associated with heart disease] declined after just a couple of years of privation. Following the war, when the food supply recovered, the atheromas came back."

Despite clues like the wartime autopsies, however, most physicians until recently believed that atherosclerotic plaque was forever. "It's an idea that has been around for at least the last half century," Dr. Blankenhorn says, "that atherosclerosis is inevitably progressive, that it's age-related, and that once it starts it is going to keep going."

Now studies by several researchers, including Dr. Blankenhorn, have refuted that notion. "Our Cholesterol Lowering Atherosclerosis Study focused on non-smoking men between the ages of 40 and 59 who had progressive heart disease and had already had bypass surgery so they wouldn't need an operation again soon. We did a baseline angiogram [an X-ray examination of blood vessels], to see what state their coronary arteries were in. Then we treated them aggressively using medications, exercise and weekly sessions with a diet counselor who kept a computerized record of what they ate. But we didn't try to restrict their diet, only to give them information so they could choose themselves.

"This was no wartime starvation regimen. These were freely living American citizens eating what they wanted. And they didn't lose pound one, on average, so you know they got plenty to eat," he says.

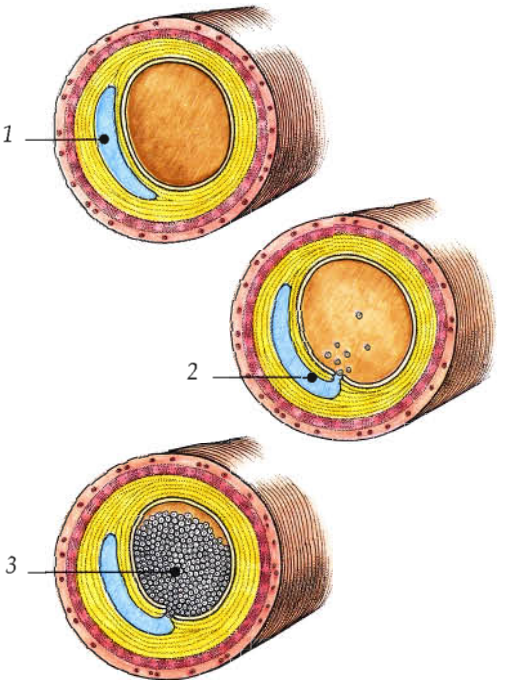
After two years, Dr. Blankenhorn and his colleagues repeated the angiographic studies to see whether the men's arteries looked better or worse. The result? Nearly one in six of them had actually lost some of their plaque, and the greatest improvement came in those who were eating the least fat.

The finding that atherosclerotic plaque can recede has now been confirmed by two other studies, one at the University of Washington that used a more aggressive drug therapy, and another at the University of California at San Francisco that employed only exercise and diet. These results imply that, under certain conditions, heart disease may be halted or even reversed.

The hitch, of course, is that not every heart patient—and virtually none of the millions of Americans who are simply at risk for heart disease—will get the same careful attention that was paid to Dr. Blankenhorn's patients. "We are kidding ourselves if we think doctors alone can spread the gospel," says Dr. John W. Farquhar of the Stanford University Medical School's Center for Research in Disease Prevention. "People don't live in doctors' offices, they live in their communities. The average person visits his doctor exactly once per year, and if you compare that 30 minutes of instruction from his physician to the thousands of hours he spends talking to friends, reading, or watching TV, you can see the problem."

Seeking to carry the message to people where they live, Dr. Farquhar and his Stanford colleagues several years ago took on a truly Herculean task. They chose five northern California cities, divided them into "treatment" and "control" groups, and set out to try to change the behavior of the more than 120,000 residents of the "treatment" cities of Salinas and Monterey. The five-year effort used a variety of educational programs to promote good health habits.

The First Moments of a Heart Attack



1. A coronary artery has been partially clogged by the gradual buildup of atherosclerotic plaque that includes a pool of semi-liquid fat along one wall. 2. The presence of the fatty liquid can concentrate stress at the edge of the plaque, enough to rupture it there. 3. Clot-promoting factors are exposed underneath, quickly causing a clot to fill the plaque-narrowed artery.

"We worked with the Stanford communication department to design programs that would take advantage of social learning theory," says Dr. Farquhar. The multimedia effort reached even into people's homes, with step-by-step kits on exercise, nutrition and smoking that people could put on their refrigerators, complete with heart-shaped

(continued on page 39)

"We are kidding ourselves if we think doctors alone can spread the gospel. People don't live in doctors' offices, they live in their communities."

(Top): The Begin and Win program, an outgrowth of Dr. John Farquhar's community-based heart disease prevention program in California, continues to attract people to its exercise programs in Monterey. (Left): A researcher examines a view of a coronary artery that shows the characteristic thickening of atherosclerosis.

A cardiovascular researcher at Bristol-Myers Squibb research facilities in Princeton, New Jersey, uses ion exchange columns to test new HMG Co-A reductase inhibitors to lower cholesterol.

Cardiovascular Research at Bristol-Myers Squibb

Company scientists screen potential new cholesterol-lowering agents using yeast strains modified by recombinant DNA technology.

Heart disease can take decades to develop, often passing through a predictable series of stages, from symptomless early conditions like high blood pressure or elevated blood cholesterol to atherosclerosis, irregular heart rhythms, heart attack, congestive heart failure and endstage heart disease.

Fortunately, this progression is not inexorable. At each step, doctors can intervene either to slow the progression of the illness or, in some cases, to halt it altogether and even reverse it. Bristol-Myers Squibb Company pharmaceuticals currently being marketed or in development are among the most potent weapons at their disposal.

One of the most important risk factors for heart disease is excess cholesterol in the blood. *Prava* (pravastatin), the company's new cholesterol-lowering agent, decreases not only total cholesterol but also the low-density lipoprotein (LDL) fraction thought to be most harmful.

Prava is a new member of the class of anti-cholesterol drugs that work by blocking an enzyme known as HMG Co-A reductase, important in synthesizing cholesterol. It works primarily in the liver and ileum, the two major sites in the body for cholesterol production.

A study in Scotland also is examining whether *Prava* can help prevent first heart attacks and premature death. Two other studies are measuring its benefits for people who have already had a heart attack.

In the company's drug development pipeline are other lipid-lowering agents including a novel HMG Co-A reductase inhibitor, BMY 22566, and compounds designed to block later steps in the pathway of cholesterol synthesis, inhibiting cholesterol production without affecting other important products of the HMG Co-A reductase enzyme.

Questran is cholestyramine, the company's lipid-lowering agent often used as a drug of first choice for cholesterol-reducing therapy. The company has filed for approval to market a tablet form of *Questran*.

Another very common risk factor for cardiovascular disease is high blood pressure. Here the company's leading drugs include *Capoten* (captopril), the first blood pressure medication to work by inhibiting the angiotensin converting enzyme (ACE). Awaiting approval in many markets is a second-generation ACE inhibitor, *Monopril* (fosinopril), with its convenient once-a-day dosage that should be effective and safe in a variety of patient populations.

Company researchers also are seeking novel ways to achieve the same effect as *Capoten* without actually interfering with the angiotensin converting enzyme. One group of compounds under study works by preventing the blood vessels from responding to angiotensin II, a powerful vasoconstricting substance that results from ACE action.

ACE inhibitors may be useful against many conditions besides high blood pressure. At Harvard Medical School, for example, investigators are studying whether *Capoten* might help prevent certain damaging changes in heart structure, called remodeling, that occur after a heart attack. Other scientists are testing whether *Capoten* could ameliorate the progressive kidney failure suffered by many diabetics. *Capoten* is considered particularly promising for diabetics since, unlike diuretics and beta blockers, it decreases the body's resistance to insulin.

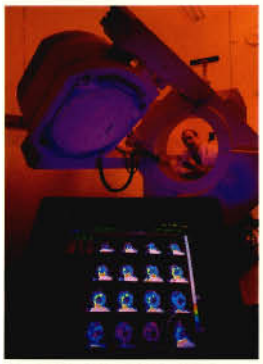
If risk factors like cholesterol or high blood pressure are left unchecked, they can lead to atherosclerosis, or the accumulation of fatty, fibrous deposits on artery walls. Both *Capoten* and *Prava* play a role here, discouraging plaque formation by controlling blood pressure and elevated cholesterol, respectively. Researchers are exploring the possibility that *Prava* and *Questran* may help clear away established plaques in some patients.

They are also pursuing other leads that may produce new agents to control plaque formation. One line of investigation seeks to prevent the modification of LDL cholesterol and the subsequent incorporation of modified LDL into plaque. Another is searching for a way to block the aggregation of the clot-promoting cells called platelets at the plaque site, since they seem to contribute to the atherosclerotic process. One simple agent that may be effective is aspirin (*Bufferin*). In 1985, the FDA approved the use of one aspirin tablet a day with a physician's advice for people who already had experienced a heart attack or unstable angina to reduce the risk of a second heart attack.

Cardiovascular Risk Management

Atherosclerosis

The company has a number of compounds that help reduce the cholesterol that causes atherosclerosis, including *Prava* and *Questran*. Clinical trials are underway to study the effectiveness of *Prava* and *Questran* in reducing existing atherosclerotic lesions and preventing new lesions. The company's diagnostic imaging agents, including *Isovue*, *CardioGen-82* and *CardioTec*, can help determine the extent of the blockages.



Researchers are seeking new radiopharmaceuticals to diagnose cardiovascular conditions using MRIs, as well as PET scanners like the one shown here.

A radiographic image analyzer is one of a number of new tools that aid in the identification of new compounds that will treat or prevent atherosclerosis.

LVH

Left ventricular hypertrophy (LVH) occurs when hypertension causes the left ventricle of the heart—the pumping chamber—to thicken and pump less efficiently. The company's two ACE inhibitors, *Capoten* and *Monopril*, can stabilize or reduce left ventricular mass.

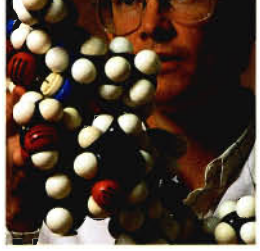
Studies of the effects of new compounds are made using a myograph isolated tissue bath, in which a bit of heart tissue is immersed in a solution containing the new compound.

Refrigerated chromatographic columns are used to isolate and purify hormone receptors. Such techniques aid in discovering drugs to block receptors in the treatment of cardiac hypertrophy and hypertension.

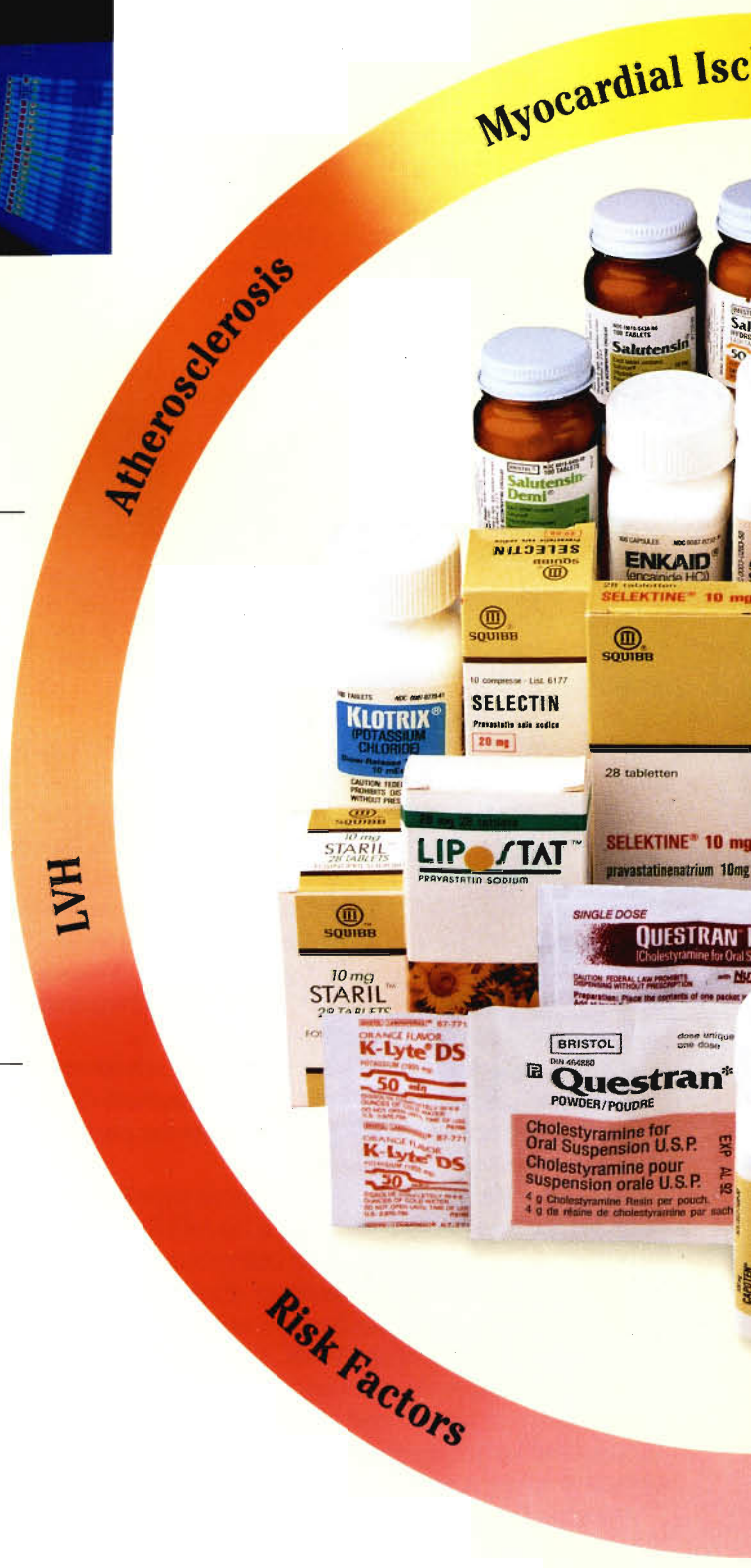
Risk Factors

High blood pressure, high cholesterol levels, insulin resistance and diabetes are the key risk factors to be dealt with to prevent the onset of a number of serious cardiovascular disorders. Bristol-Myers Squibb products that help include antihypertensive drugs like *Capoten*, *Monopril*, *Corgard*, *Capozide* and *Sotacor*, and cholesterol-lowering agents like *Prava* and *Questran*. In clinical trials, *Capoten* seems to have a beneficial effect on insulin resistance, where the body is unable to use glucose properly.

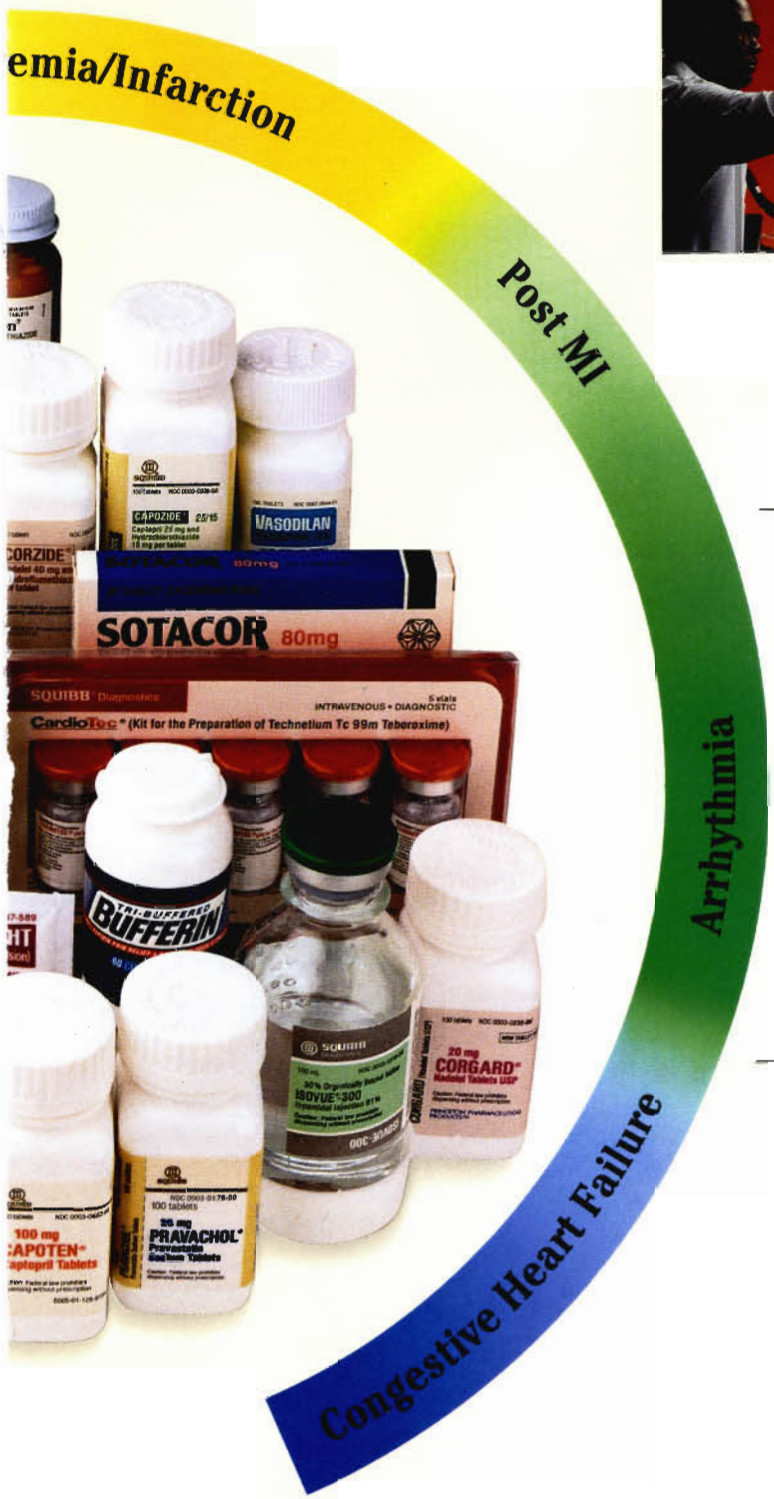
The metabolites of a novel therapeutic agent are analyzed using liquid chromatography and mass spectrometry.



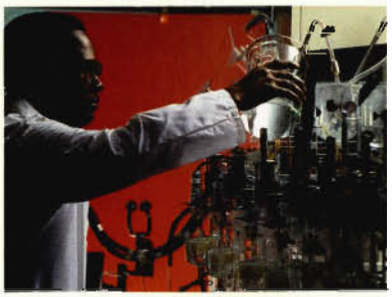
An understanding of the molecular makeup of endothelin, implicated in hypertension and ischemia, could lead to new compounds that would interfere with its production or block its effects.



Cardiovascular risk management was first conceptualized at Harvard Medical School by Drs. Eugene Braunwald and Victor J. Dzau. It stresses the need to go beyond the treatment of isolated cardiovascular disorders and instead to consider the chain of events triggered by risk factors, leading to more serious cardiovascular disorders and eventually, to endstage heart disease. Bristol-Myers Squibb has developed and is researching products aimed at reducing risk factors and treating the various cardiovascular disorders at every point in the process.



Post MI



To develop new antithrombotic and antihypertension medicines, scientists study the mechanical responses of the vascular system to new compounds.

CardioGen-82 is the first radiopharmaceutical approved by the FDA for use in PET scanners to diagnose heart disease.

Researchers are seeking to determine whether *Capoten* may reduce mortality in patients who have had a heart attack or myocardial infarction (MI). Under a physician's supervision, *Bufferin* has been approved to help prevent a second heart attack. Diagnostic imaging agents, including *CardioGen-82* and *CardioTec*, are used to study damage after an attack. Beta blockers, including *Corgard* and *Sotacor*, are used in patients to help slow the heart rate in a damaged heart.

Arrhythmia

New agents are being developed to help control irregular heartbeats. Here scientists assess the value of new agents on irregularities in heart rhythm.

Single crystal X-ray diffraction is used to determine the precise geometry of new cardiovascular drugs.

Irregular heartbeats, or arrhythmias, can occur at any time, triggering cardiac arrest. Among the company's products to treat arrhythmias are *Betapace*, currently awaiting FDA approval and already marketed outside the U.S. as *Sotacor*, a beta blocker with unique antiarrhythmic qualities, and *Enkaid*, for treating life-threatening arrhythmias.

Congestive Heart Failure

A chemist completes the synthesis of a potential drug to treat congestive heart failure.

Chemists determine the molecular structures of new drugs using an NMR (nuclear magnetic resonance) device.

Capoten was the first agent in over 30 years to be approved for the treatment of heart failure, a condition in which the heart fails to pump efficiently. ACE inhibitors have been shown to reduce symptoms, improve exercise capacity and reduce mortality. *Capoten* is the leading ACE inhibitor in the treatment of heart failure. In addition, the company markets potassium supplements, including *Klotrix* and *K-Lyte*, often used by heart failure patients who must take diuretics.

Doctors are increasingly using the imaging agent *Isovue* to spot blockages in the coronary arteries. Last year, the American College of Radiology expanded its endorsement of nonionic contrast media like *Isovue*.

Several new Bristol-Myers Squibb agents offer the promise of detecting coronary artery blockages well before they cause symptoms. Usually, a coronary artery may be about 80 percent blocked before the patient begins to feel the pain called angina, and then only when he is exerting himself. But using one of the company's radiopharmaceutical imaging agents, *CardioGen-82*, in conjunction with a positron emission tomography (PET) scanner, doctors have been able to spot occlusions as small as only 40 percent. *CardioTec*, approved for marketing by the FDA in December 1990, and used with gamma cameras, is the first of a new class of imaging agents indicated for myocardial perfusion studies, measuring blood flow to the heart.

While atherosclerosis may lay the groundwork for a heart attack, the attack itself is usually caused by a sudden clot in one of the coronary arteries that supply blood to the heart. Many company efforts seek to prevent first or subsequent heart attacks by interrupting the clotting process.

An early step in clot formation is the aggregation of platelets, so researchers are investigating several ways to prevent this. One group of compounds under study at Bristol-Myers Squibb mimics a natural anti-aggregating compound called prostacyclin, which is made by blood vessel walls. Another approach being studied by company scientists is to inhibit an enzyme called phosphodiesterase that is required for platelets to clump together.

Yet another method seeks to block the receptor for thromboxane, a pro-aggregating substance made by the platelets themselves. Under development is SQ 30741, a thromboxane receptor antagonist which blocks the vasoconstriction and platelet aggregation effects of thromboxane. Separate company research efforts also are aimed at influencing coagulating factors that are not controlled by platelets.

During a heart attack, blood stops flowing to a portion of the heart muscle. The tissue in that area is injured or dies. Company researchers are working on potassium channel activators that would prevent one cause of this harm, an excess buildup of calcium ions in the blood-starved cells. Its researchers also are looking for ways to block endothelin, a natural substance which may be produced in excessive amounts during or after an attack.

Another manifestation of heart disease is irregularities of heartbeat, called arrhythmias. The company already markets *Enkaid* to treat life-threatening arrhythmias. It is now awaiting FDA approval of *Betapace* (sotalol) as an antiarrhythmic. *Betapace*, a beta blocker with special antiarrhythmic properties, already is marketed as *Sotacor* elsewhere in the world.

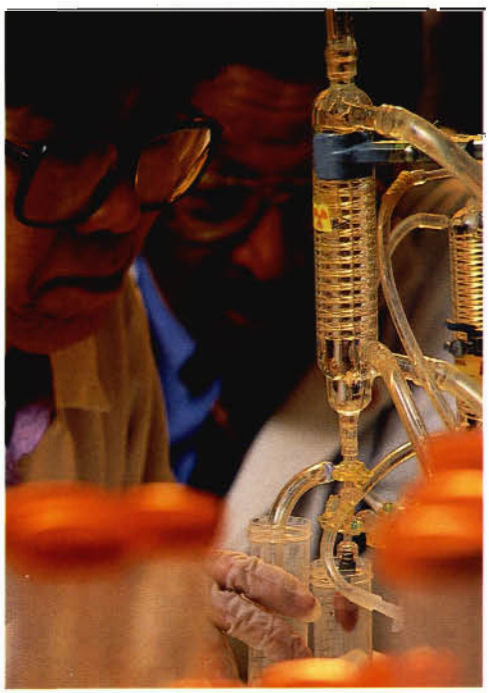
After a heart attack, the challenge is to prevent a new attack from occurring and to help the injured heart cope. During the 1980s, extensive studies showed that daily aspirin could help prevent both second heart attacks and so-called transient ischemic attacks—precursors to stroke—in men. Studies like those at Harvard now are examining how ACE inhibitors provide important help for the weakened heart and whether HMG Co-A reductase inhibitors might prevent a second heart attack.

CardioGen-82 and *CardioTec* may prove valuable in determining how severe a heart attack has been. Both are taken up by normal but not by damaged myocardial tissue. Because both radiopharmaceuticals emit tiny amounts of radioactivity, their distribution can be detected outside the body by scanning devices, helping to assess the extent of myocardial destruction. Earlier radiopharmaceuticals had to be made at a cyclotron or reactor and then transported to the hospital for use. But since both *CardioGen-82* and *CardioTec* are generated at the imaging site, they can have extremely short half lives—76 seconds and six hours, respectively—speeding the process of taking successive scans while improving patient safety.

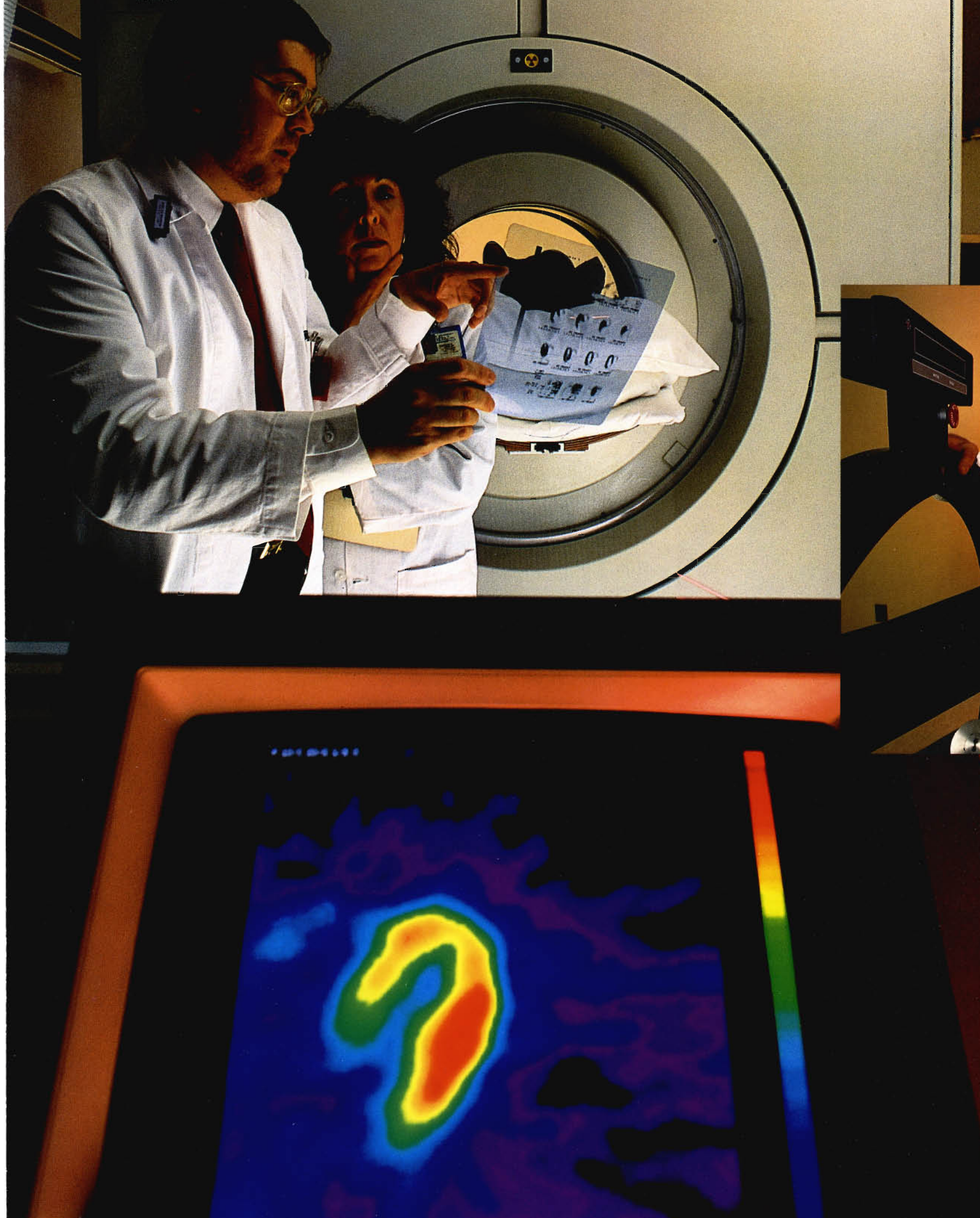
If the heart is badly weakened, by a heart attack or other disease processes, some patients suffer from congestive heart failure, where the organ can no longer pump enough blood. *Capoten* is approved for the treatment of congestive heart failure. Doctors use it to dilate blood vessels and thus ease the load on the heart. Several clinical trials are ongoing using *Capoten* to treat patients right after a heart attack to assess whether it can slow the progression of cardiovascular disease.

Company researchers also are exploring a different way to lessen the demand on the heart. They are studying atrial natriuretic peptide (ANP), a hormone-like substance made by the walls of the heart. ANP seems to be the heart's natural SOS signal: it causes blood vessels to dilate and the kidneys to dump salt and fluid, so that the strain on the heart is relieved. One compound under study is a potent inhibitor of the principal enzyme that breaks down ANP. Scientists hope to use this substance to help the failing heart get its life-saving message through. ■

The inhibition of the angiotensin converting enzyme is studied in developing drugs to treat cardiac hypertrophy.



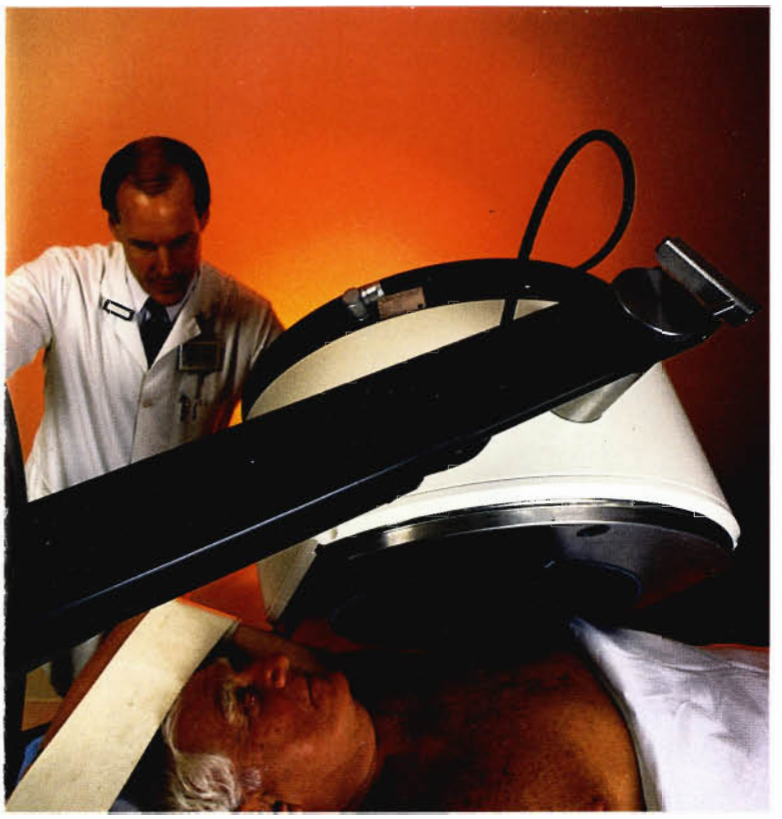
A Bristol-Myers Squibb researcher works behind a beta shield to protect her from low level nuclear tracers in test tubes. She is studying how new compounds under development bind to radioactively labelled receptors.



magnets. "We figured the refrigerator is one of the few remaining points of communication in America—you know, the place where you leave messages like 'Take out the garbage' or 'Feed the cat.' People don't get together as families any more but they do look at the refrigerator," says Dr. Farquhar.

After five years, people in the "treatment" cities had achieved a two percent reduction in blood cholesterol, a four percent reduction in blood pressure, a three percent cut in resting pulse rate and a sharp 13 percent decline in smoking when compared to people in the "control" cities of Modesto, Santa Maria and San Luis Obispo.

"These would be modest gains in a single individual," says Dr. Farquhar, "but spread over 120,000 people, result in about a 15 percent reduction in risk of cardiac death—which translates into a lot of lives saved. And the cost was only $2.68 per person per year, compared to the $200 per person per year that Americans spend buying cigarettes."



(Left): Dr. Richard Brunken reviews the PET scans of a patient with heart failure at the Ahmanson Biochemical Imaging Center at the UCLA School of Medicine in Los Angeles.

(Top): Single photon emission computed tomography (SPECT), using radiopharmaceuticals, offers a non-invasive means to measure myocardial perfusion, or blood flow, to the heart muscle in the diagnosis of coronary artery disease.

Tracking a Moving Target

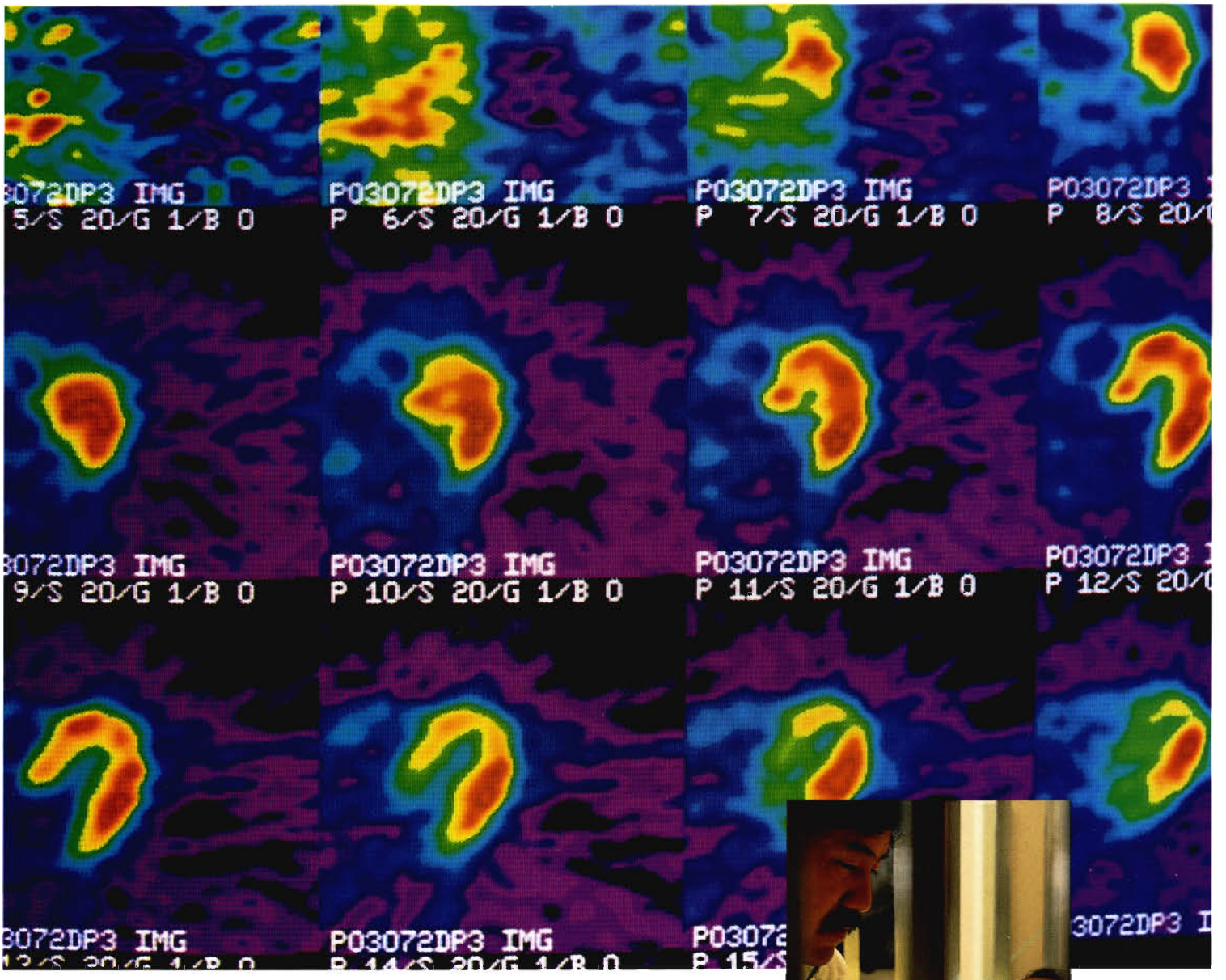
"We already know enough to change the risk factors of heart disease," says Dr. Farquhar. "What we need now is a fast, non-invasive way to tell who has lesions, so we can start treating them before they cause symptoms." Today, the most common way to spot atherosclerosis is with angiography. Physicians thread a catheter through the circulatory system and then inject a dye that makes the coronary arteries visible on an X-ray. But angiography is uncomfortable and somewhat risky, so it isn't used unless doctors strongly suspect a patient is ill.

Scientists have been held back in using more sophisticated imaging devices, like the computed tomography (CT) scanner, to study the heart in part because it is always beating 60 to 80 times a minute and presents a moving target that shows up as a blur on most CT machines. Also, the resolution of the machines has not been sharp enough to show the relatively tiny coronary arteries.

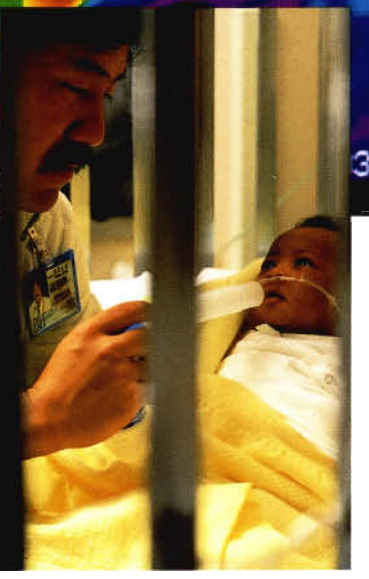
But with the aid of new technology, scientists are overcoming those obstacles. One innovation is the rapid, or cine, CT that completes an image in a tiny fraction of the time required by a conventional scanner. "In most cases of coronary artery disease, the plaque develops calcium deposits that show up nicely on cine CT," says Dr. Robert O. Bonow, Deputy Chief of the Cardiology Branch at the National Heart, Lung and Blood Institute (NHLBI) in Bethesda, Maryland. "The only question is whether the calcification starts too early or too late in the disease process for the diagnosis to be useful."

Meanwhile, researchers are working to improve the speed and resolution of other scanners—including those that rely on magnetic resonance imaging (MRI). The NHLBI recently received a special $3 million grant from

"The ultimate aim of all such cardiac imaging techniques, of course, is to do away with the uncertainty doctors face in trying to diagnose what is going on inside an ailing heart."



(Top): These cross sections of the left ventricle (horseshoe-shaped object) of the heart, taken with a PET scanner, show evidence of tissue glucose metabolism, a sign that the tissue is still viable.



(Right): Sixteen-day-old Tatiana Locke receives inhalation therapy after having surgery for a congenital defect in her aorta. Her heart was imaged with a PET scanner before and after the operation to better diagnose the disorder.

Congress to build a powerful new MRI machine specifically to take pictures of the heart. "The magnet for this scanner will be twice as strong as that in the largest clinically available systems," says Dr. Robert S. Balaban, chief of the Laboratory of Cardiac Energetics. "That will give us a higher signal-to-noise ratio, which improves the resolution per unit time. We should be able to collect an image in as little as a few milliseconds."

Scientists also are making increasing use of special MRI contrast media, analogous to the contrast dyes used for years with X-rays and CT scans. And they are exploiting so-called tagging procedures that use a variation in the device's strong magnetic field to follow the movement—sometimes in three-dimensional detail—of selected parts of the heart. "Within ten years," says Dr. Balaban, "I would expect the MRI scanner to become an integral tool in the workup of patients."

Meanwhile, standard imaging techniques have not stood still. "Echocardiography remains the most widely used technique for viewing the heart," says Dr. Bonow, "and now is used not only in resting patients but also during exercise, drug infusion and even surgery and angioplasty. Conventional nuclear medicine pictures continue to evolve with the addition of new agents based on isotopes of technetium that provide better image quality."

Angiography, still the gold standard for visualizing blockages in blood vessels, has been improved with the introduction of nonionic contrast media that cause fewer side effects than older agents.

One of the most provocative developments in imaging revolves around a recent discovery about what happens when a heart gets sick. In some patients, scientists have found, the damaged heart muscle does not die but only goes into a strange, quiescent state called hibernation. On a CT or MRI scan, this hibernating tissue appears dead, since it does not move. But if full blood flow is restored, the sleeping muscle wakes up and starts beating again.

The problem doctors now face is to distinguish which immobile tissue is hibernating—and thus might recover—and which is not. As Dr. Richard C. Brunken of the University of California at Los Angeles School of Medicine explains: "Our typical patient might be one who had a heart attack months ago and is now suffering from congestive heart failure. His cardiologists want to know whether doing coronary bypass surgery or angioplasty will help him."

To find out, Dr. Brunken and his colleagues employ a machine called a positron emission tomography (PET) scanner that can measure metabolic processes inside the heart. They first determine how much blood is flowing to the various parts of the organ. This is done using radiopharmaceuticals based on rubidium-82 or nitrogen-13 ammonia that can distinguish the pattern of blood flow. Then they measure how much of a sugar called glucose the heart is using—since hibernating tissue tends to take up much more glucose relative to its blood supply than the scar tissue that is left after heart muscle death. "In studies from this lab, the test has had an 85 percent accuracy in predicting which patients will benefit from an operation, and a 92 percent accuracy in predicting which patients won't," says Dr. Brunken. "Since any operation is a matter of risk versus benefit, this gives you a better idea of what you have to gain."

The ultimate aim of all such cardiac imaging techniques, of course, is to do away with the uncertainty doctors face in trying to diagnose what is going on inside an ailing heart. But even the best pictures imaginable could only spot heart disease in someone who is already sick. In order to anticipate which healthy people will eventually get sick, doctors must rely on the conventional risk factors for heart disease—such as a person's blood pressure, cholesterol level, smoking habits, weight, age and gender.

The problem with risk factors, of course, is that they give only the statistical odds that someone will get heart disease—and many people beat the odds. "I sometimes use Winston Churchill as an example," says Dr. Jan Breslow of Rockefeller University in New York. "He smoked, drank, ate too much and still lived to a ripe old age. The opposite of that might be somebody like Arthur Ashe, a professional tennis champion who lived a healthy lifestyle and still had two bypass operations before he turned 40."

How can one person flout danger and get away with it while another succumbs prematurely? Part of the answer, scientists believe, lies in our genes. For more than a decade, Dr. Breslow's lab and other research groups have worked to identify and characterize the genes that govern fat metabolism, and thus influence susceptibility to heart disease. Dr. Breslow cites the example of the gene for a protein called apolipoprotein B (or apo B). This protein is a key constituent of so-called low-density lipoprotein cholesterol (LDL cholesterol), often called the "bad" cholesterol because too much of it raises the risk of heart disease. Researchers at another lab found that about one American in 500 possesses a mutant form of the apo B gene that makes it hard for the body to clear LDL cholesterol from the blood, thus raising the risk of heart attack. But Dr. Breslow's lab has published evidence that some 10 to 20 percent of people have more subtle mutations in their apo B genes that affect LDL processing.

Not all the mutations are bad. Dr. Breslow and his colleagues have identified at least one apo B variant, possessed by about one American in 1,000, that actually *reduces* LDL levels. "That may be the Winston Churchill gene," Dr. Breslow jokes, "since it probably protects people against heart disease. The upper normal LDL level in our society is around 140 milligrams per deciliter of blood. These people might have LDL levels of only 40 or 50.

"I don't think genetic testing will ever replace screening for cholesterol and other risk factors, the way we do today. What genetic tests will do is further refine the predictive value of those measurements and help identify susceptible people as early as childhood. In every individual, there is a balance between genetic susceptibility and lifestyle. In some, the genetic factors are extremely strong, so that almost no matter what they do they will probably get a heart attack. But in others, if they know from the outset that they are susceptible and so they lead a good lifestyle, they might avoid it altogether."

A Strong and Deadly Gene

The patient, a French-speaking Canadian in his 40s from a little town more than an hour east of Montreal, seemed too young to have such severe heart disease. His heart muscle had enlarged to the point where it was intruding into the pumping chambers within, preventing the heart from working right.

Dr. Jules Arthur "Peter" Paré, of Montreal's Royal Victoria Hospital, was only 40 when he first saw the man in 1957. And Dr. Paré might well have forgotten him, had it not been for a chance occurrence that later proved crucial in discovering the cause of the bizarre defect. As Dr. Paré, now 73, recalls: "At about the same time, I was called in as a consultant for a patient at another hospital who was suffering a similar heart problem. To my great surprise, this second man turned out to be the brother of the first. We spent some time talking to both of them. What we heard was a remarkable history of people in their family dying suddenly at very young ages."

The two brothers were among 13 children from a family so beset by heart disease that the local doctors referred to it with grim humor as a curse. Not everyone was affected. But those who were always died prematurely—such as the young boy who dropped dead one morning on his way to school. With a team of specialists, Dr. Paré traveled to the town and examined over 70 family members—one-third of whom turned out to have the condition.

The family's disease, although it goes by the tongue-twisting name of hypertrophic cardiomyopathy, is actually one that most people have heard of—though they may not realize it. This condition, sometimes hereditary and sometimes not, is a leading cause of sudden death in young athletes. Among its recent victims: Hank Gathers, the talented player for Loyola Marymount's basketball team, who collapsed during a championship game last year.

"Unlike many heart conditions, which affect mainly the elderly, this one often affects the young," says Dr. Christine E. Seidman, a cardiologist at Brigham and Women's Hospital in Boston. "People who may not know that anything is wrong with them suddenly drop dead. That is just plain hard to forget, when you see it.

"I had been interested in this disease for a long time," she says, "because hypertrophy—or abnormal enlargement—is one of the most common ways the heart can fail. Not many people have the hereditary form of the disease. But I thought that by understanding the hereditary form, we might get clues to the more common forms that are secondary to high blood pressure or atherosclerosis."

In seeking the cause of the condition, Dr. Seidman had a special advantage: her husband, Dr. Jonathan G. Seidman, is a geneticist at Harvard Medical School and an investigator at the Howard Hughes Medical Institute. His lab specializes in the genetic analysis needed to track down errant genes. "But to do so, we had to study a large family suffering from the disorder," Dr. Jonathan Seidman explains. "When they found the locus of the Huntington's chorea gene, for instance, they used a large number of related people living in Venezuela. In searching for other genes, we geneticists have also relied on other groups that have big families, like the Amish and the Mormons."

Digging through the medical library, Dr. Christine Seidman came across a 1961 paper by Dr. Paré. "I called Peter and he was delighted," she says. "With his help, and that of a translator from his lab since I don't speak French, we made contact with family members and collected blood samples from 78 of them." They also made a sad discovery: in the years since Dr. Paré's first visit, nearly two dozen additional people had died—almost all of heart disease before they were 45 years old.

Armed with the blood samples, the Drs. Seidman and their colleagues grew cultures of cells from each patient and extracted the DNA. Then they cut the DNA with special enzymes. By examining the pattern of cuts, they determined that a peculiar genetic pattern turned up in everyone suffering from the defect. "The odds that this result could be just due to chance were a very reassuring billion to one against," Dr. Jonathan Seidman says.

Eventually, the scientists isolated and sequenced a mutant gene. "It turned out to be a change in a single base pair of one of the genes for cardiac myosin, a special type of myosin found only in heart muscle," he adds. "It was a mutation that had never been seen before, even in myosin genes from rats, mice, chickens, fruit flies, sea nematodes and amoebae. That is very strong evidence that the mutation is responsible for the defect."

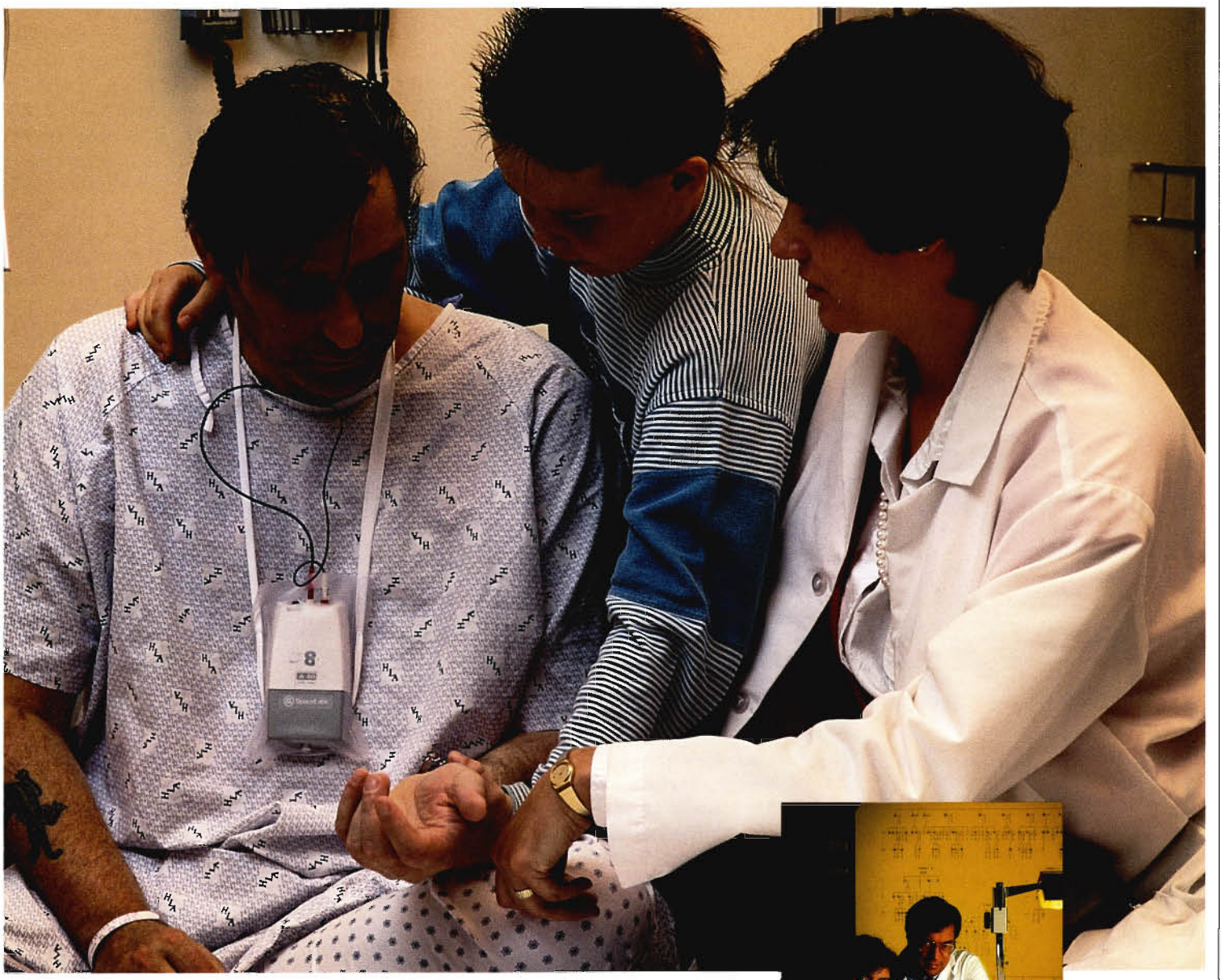
Even before the news of the discovery was published in The New England Journal of Medicine, the scientists had the pleasure of telling the family members that they had found the cause of the mysterious curse. The interviews were sometimes poignant. "One of the most amazing cases," says Dr. Christine Seidman, "was of a gentleman in his 50s whom Peter had seen years before. At that time, Peter told the man that he did not think he had the defect. But the man's mother died of heart disease, his sister died at a cousin's funeral, and he was convinced he was affected—so he opted to marry late in life and have no children.

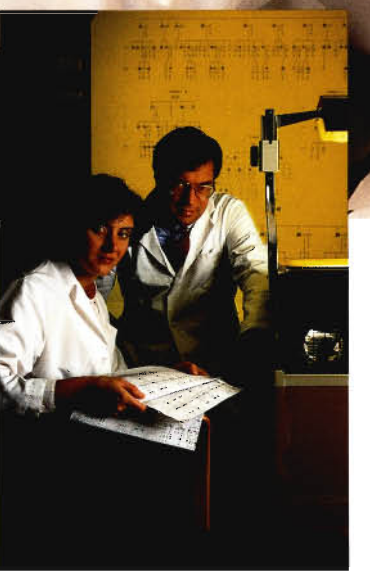
"When I told him that not only was he not affected but that we could prove it by his genotype, he sat in the office and cried for what he had lost."

Fortunately, for members of the Canadian family, and for many others affected with defective cardiac myosin genes, the discovery marks a major step towards a day when such tears will no longer be shed. The identification of the gene provides a powerful tool for diagnosis. And, it gives clues that could lead to discovery of a cure.

"When you do genetic analysis," Dr. Christine Seidman observes, "you sketch out the family tree on a big piece of paper and blacken in the individuals who have the defect and put a slash through any who are dead. On this family's pedigree, you see many blackened and slashed individuals. I hope it will give them some consolation to know that, thanks to their help, the day may come for future generations when no one will be blackened or slashed." It is a hope that scientists in all fields of cardiovascular research passionately share. ■

"Not everyone was affected. But those who were always died prematurely..."



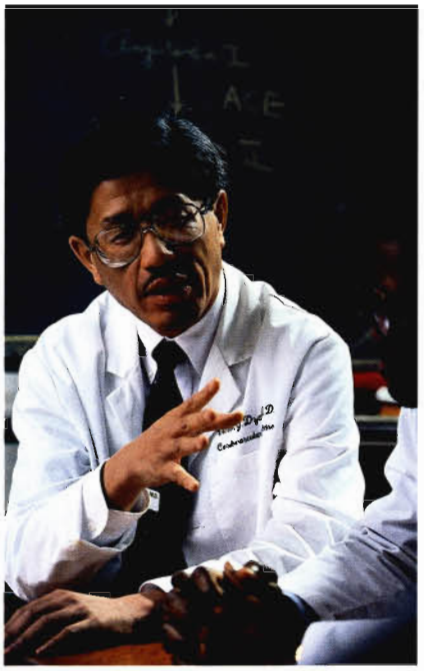


(Above): 42-year-old William Willis suffers from familial hypertrophic cardiomyopathy. He is awaiting a heart transplant. His 10-year-old son, William, Jr., also has the gene responsible for this sometimes fatal defect. Here he is seen with Dr. Christine Seidman, a researcher and cardiologist. (Right): Drs. Christine and Jonathan Seidman hope that someday, by analyzing the pedigrees and genetic makeup of families with hypertrophic cardiomyopathy, they will be able to understand the more common forms of hypertrophy, a condition where the heart muscle thickens and functions abnormally.

Programs of Public Interest

Bristol-Myers Squibb Announces New Cardiovascular Research Grants Program

In early December, 1990, Bristol-Myers Squibb Company announced the creation of a new unrestricted biomedical research grants program—to fund basic cardiovascular research. This $2.5 million program is the sixth no-strings-attached grants program funded by the company since 1977. In total, the company now has committed more than $29 million in unrestricted support of cancer, nutrition, orthopaedic, neuroscience, pain and now cardiovascular research, with grants to medical schools and research institutions in North America, Europe and Asia.



Dr. Victor J. Dzau, chief of Stanford University's Division of Cardiovascular Medicine, is known for his work on the causes of hypertension. His research group is one of five to receive the first Bristol-Myers Squibb no-strings-attached grants in support of cardiovascular research.

The cardiovascular program will provide five leading research institutions with grants of $100 thousand a year for five years.

The initial grantees include: University of California, San Francisco, to support research on the impact of growth factors on cardiovascular disease and the microbiology of the cardiovascular system; University of Washington, Seattle, to further exploration of the process of atherosclerosis and the hyperproliferation of vascular smooth muscle; Baylor College of Medicine, Houston, for the study of the mechanisms of hypertension, focusing on vascular regulation and endogenous relaxation and constriction substances in the body; Harvard Medical School, Boston, Massachusetts, for investigations of the genetic causes of heart disease, including work in cloning the ANF gene, an important hormone secreted by the heart, and familial hypertrophic cardiomyopathy, an enlargement of the heart that can lead to sudden death; and Stanford University, Stanford, California, to further research on hypertension, with a particular focus on the renin angiotensin system. In each case, as with all the company's unrestricted biomedical research programs, institutions have the right to redirect and allocate the funds as they see fit.

In addition to the grants, the program also includes the annual Bristol-Myers Squibb Award for Distinguished Achievement in Cardiovascular Research, the first of which will be presented in 1991, and annual symposia in the field organized by participating grant institutions.

Other Unrestricted Medical Research Grants

In 1990, two new unrestricted cancer research grants, totaling $1 million, were announced: Vincent T. Lombardi Cancer Center at Georgetown University Medical Center, and the Foundation for the Promotion of Cancer Research in Tokyo, to benefit Japan's National Cancer Center. Total funding committed to the program since its inception in 1977 now exceeds $13.3 million.

The thirteenth annual Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research was presented in 1990 to Dr. Bert Vogelstein of Johns Hopkins University, Baltimore, Maryland, for defining a sequence of genetic events that are responsible for the formation and growth of colon cancer.

During 1990, the company sponsored two Bristol-Myers Squibb Symposia on Cancer Research. In May, the Japanese Foundation for Cancer Research in Tokyo organized "Drug Resistance as a Biochemical Target in Cancer Chemotherapy." In September, Massachusetts Institute of Technology organized "Nuclear Processes and Oncogenes."

The nutrition grants program celebrated its tenth anniversary during 1990. The tenth annual Bristol-Myers Squibb/Mead Johnson Award for Distinguished Achievement in Nutrition Research was awarded to Dr. Donald Zilversmit of Cornell University, Ithaca, New York, for his discoveries of lipid transfer proteins and his contributions to a better understanding of the atherosclerotic process.

The University of Texas and Indiana University were added to the unrestricted nutrition grants program. Total funding for the program since its inception is $5 million.

"The Biology of Feast and Famine: Relevance to Eating Disorders," the tenth annual Bristol-Myers Squibb/Mead Johnson Symposium on Nutrition Research, was organized by Toronto University.

The company has committed $3.3 million to the neuroscience research grants program since it was begun in 1988.

In 1990, the Center for Neurological Diseases at Boston's Brigham and Women's Hospital was added to the program, to support its research on the diagnosis and treatment of Alzheimer's disease.

The third annual Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience Research was presented in June to Dr. Jean-Pierre Changeux of the College of France and the Institut

Pasteur, in Paris, Dr. Bertil Hille of the University of Washington School of Medicine in Seattle, and Dr. Erwin Neher of the Max Planck Institute in Goettingen, Germany. They were selected for their pioneering contributions to understanding ion channels and the protein pores through which nerve and muscle cells communicate.

The second annual Bristol-Myers Squibb Symposium on Neuroscience Research, on "Plasticity and Pathology in the Damaged Brain," was jointly organized by the University of California, San Diego, and the University of California, Irvine.

An unrestricted pain research grant was awarded in 1990 to the University of California, San Diego, to support the study of new pain-killing drugs that bypass the brain and act in the spinal cord or other injury site. Total funding committed to the pain research program since it began in 1988 is more than $2.2 million.

Natasha Benson is being supported in her MBA degree program at Columbia University School of Business with a minority fellowship from Bristol-Myers Squibb Company.

Dr. Jean-Marie Besson of the Institut National de la Sante et de la Recherche Medical in Paris, received the third annual Bristol-Myers Squibb Award for Distinguished Achievement in Pain Research for his contributions to the effort to create non-opiate, non-addictive, pain-killing drugs as effective as morphine but free of its side effects.

The orthopaedic research grants program, initiated in 1983 and expanded in 1987, is sponsored by Bristol-Myers Squibb and Zimmer, in conjunction with the Orthopaedic Research and Education Foundation. During 1990 two new grant recipients were announced: Columbia University in New York City and Rush Presbyterian/St. Luke's Medical Center, Chicago, Illinois. Total funding for the program since it began is $3 million.

Dr. Henry J. Mankin, of Harvard Medical School and Massachusetts General Hospital, Boston, received the third annual Bristol-Myers Squibb/ Zimmer Award for Distinguished Achievement in Orthopaedic Research for his research on the molecular structure of bone cartilage and improved treatments for bone cancer.

Equal Employment Opportunity

Bristol-Myers Squibb Company is committed to ensuring equitable representation of women and minority group members at all levels of job responsibility. Currently, 33.7 percent of the company's professional and managerial employees in the U.S. are women and 12.4 percent are minority group members. For a copy of the company's most recent report on its equal opportunity policy and initiatives, write to Communications Services, Bristol-Myers Squibb Company, 345 Park Avenue, New York, NY 10154.

Programs for Women and Minorities

The company supports a variety of programs to help advance women, minorities and the disabled in their career goals. It provides direct grants and scholarship assistance to educational institutions to support scholarships and fellowships for women and minorities. It also helps fund community programs for women, minorities and the disabled to aid them in their careers.

Alternatives to Animal Testing

Bristol-Myers Squibb Company has long been involved in the search for non-animal tests to lessen its reliance on animal testing methodologies for product development and safety testing. Currently over 99 percent of the animals used in the company are for the development and safety testing of pharmaceutical and health care products.

The company is committed to a program of evaluating the usefulness of commercially available non-animal tests for in-house applications. In addition to its own efforts to develop alternatives to animal testing, the company has placed grants totaling more than $1 million to support other research initiatives in the field.

Bristol-Myers Squibb each year also sponsors a companywide symposium on non-animal alternatives. In 1990 it focused on "Managing Safety Evaluations into the 1990s."

Bristol-Myers Squibb Foundation

Charitable contributions from the Bristol-Myers Squibb Foundation, the company, its subsidiaries and divisions, and the Mead Johnson Foundation, totaled more than $17 million. Health-related, medical research and community service organizations received 51 percent of combined company and Foundation contributions; educational institutions and education-related programs received 30 percent; and civic and cultural activities received 19 percent.

Financial Review

Summary

Bristol-Myers Squibb achieved record sales and earnings in 1990. Sales increased 12% to $10.3 billion. Domestic sales, which comprised 61% of total sales, increased 7%, while international sales increased 20%. Excluding the 1989 charge of $855 million for integrating operations and for merger related expenses, earnings before income taxes increased 18% and net earnings increased 21% over the prior year, and earnings per share increased to $3.33 from $2.75.

Cash provided by operating activities continued to support increased dividend payments and to finance research, new product development and introductions, capital spending and working capital needs. The company increased dividend payments on common stock for the eighteenth consecutive year, achieving a compound annual growth rate of 18% during the past ten years. Over the same period, sales and net earnings have grown at a compound annual growth rate of 10% and 17%, respectively.

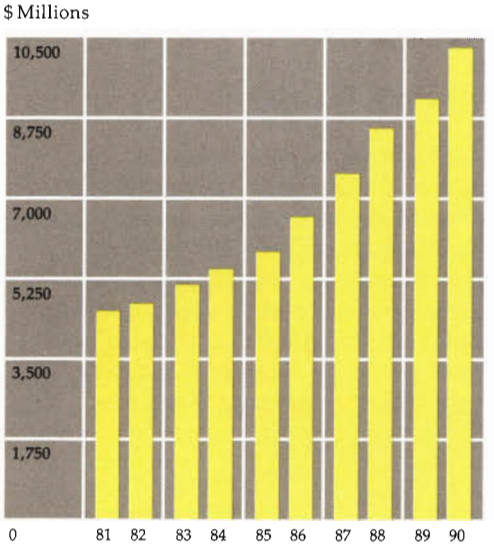
Net Sales and Earnings

Worldwide sales increased 12% in 1990 to $10.3 billion compared to increases of 7% and 13% in 1989 and 1988, respectively. The 1990 consolidated sales growth resulted from volume increases of 6%, price increases of 4% and an increase of 2% due to favorable foreign currency translation. In 1989, the increase in sales was attributable to approximately 6% of volume growth and 3% of price increases, partially offset by a 2% decline due to unfavorable foreign currency translation. Domestic operations reported sales growth of 7% in 1989 versus 8% in 1988, while international operations reported sales growth of 8% and 24% in 1989 and 1988, respectively.

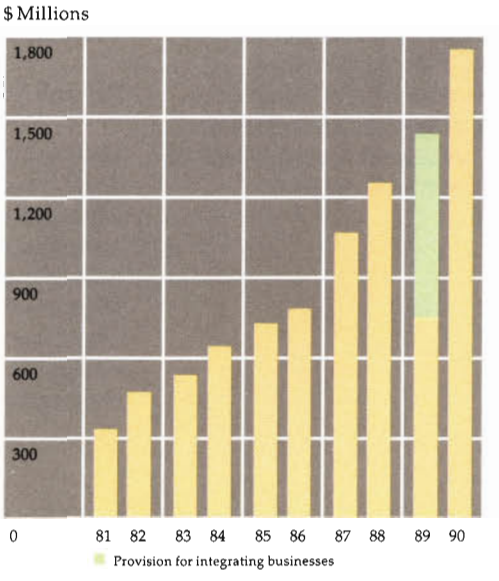
Net earnings and earnings per share in 1990 increased to $1,748 million and $3.33 per share from $747 million and $1.43 per share in 1989 and $1,254 million and $2.39 per share in 1988. Excluding the 1989 charge of $855 million for integrating operations and for merger related expenses, both net earnings and earnings per share increased 21% over the prior year. Net earnings margin increased to 17.0% in 1990, from 15.7% in 1989, excluding the costs of integration and merger related expenses, and 14.7% in 1988. Foreign exchange negatively impacted net earnings by $.14 per share in 1990, $.08 per share in 1989 and $.07 per share in 1988, primarily due to unfavorable exchange rates in highly inflationary countries.

In 1990, the effective income tax rate was 30.8% which reflects the continuing decline in foreign tax rates. In 1989, the effective tax rate was 41.5%

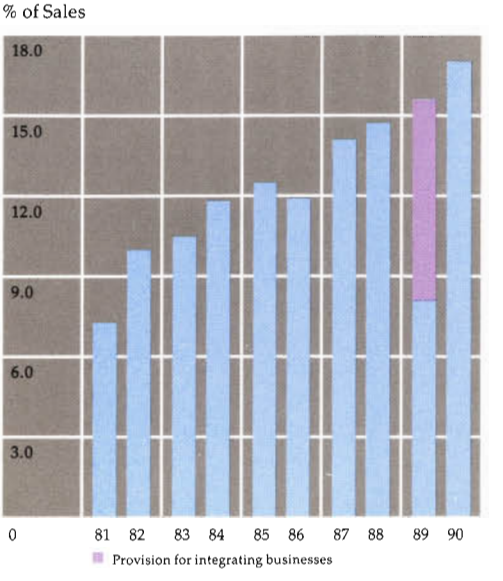
Net Sales



Net Earnings



Net Earnings Margins



which was adversely affected by integration and non-deductible merger expenses, and in 1988 the rate was 33.6%.

In December 1987, the Financial Accounting Standards Board issued Statement No. 96, Accounting for Income Taxes, which requires a change in the method of accounting for income taxes. This statement, as amended, requires the change for fiscal periods beginning after December 15, 1991. Had the company adopted this Standard in 1990, the effect on the financial statements would not have been significant. In December 1990, the Financial Accounting Standards Board issued Statement No. 106, Employers' Accounting for Postretirement Benefits Other Than Pensions. This statement requires that postretirement health costs be recorded in the financial statements as earned by the employee, and must be adopted for fiscal periods beginning after December 15, 1992. The company is reviewing the requirements of this statement and, accordingly, the effect of adopting this Standard is not currently determinable.

Expenses

Total costs and expenses were 75.5% of sales in 1990 compared to 76.8% in 1989, excluding the 1989 charge of $855 million for integrating operations and for merger related expenses, and 77.9% in 1988. In 1990, cost of products sold as a percentage of sales decreased again, improving gross margin for the ninth consecutive year. The gross margin increased to 72.1% from 71.1% in 1989 and 71.0% in 1988, as a result of favorable product mix and improved manufacturing efficiencies.

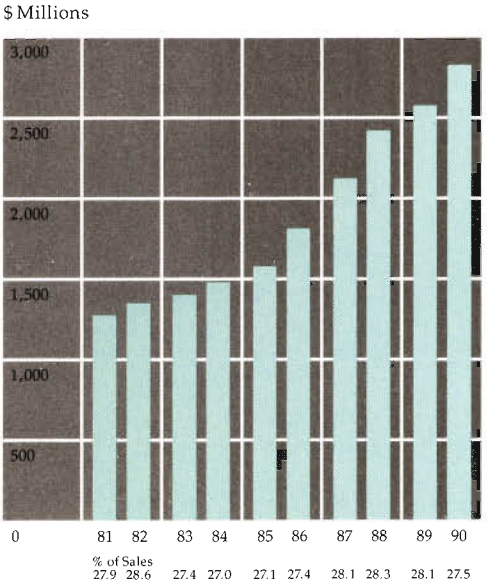
Marketing, selling and administrative expenses, as a percentage of sales, were 27.5% in 1990 compared to 28.1% in 1989 and 28.3% in 1988, primarily due to the favorable impact of administrative cost containment programs. The level of advertising and product promotion expenditures in support of new and existing products increased 8% to $1,328 million compared to $1,226 million in 1989 and $1,191 million in 1988. Since 1980, advertising and product promotion expenses have more than doubled.

Research and development expenses increased 12% in 1990 to $881 million, following increases of 15% and 22% in 1989 and 1988, respectively. Over the last ten years, research and development spending has increased at a compound annual growth rate of 16%. Pharmaceutical research and development spending increased 16% in 1990, 18% in 1989 and 24% in 1988, and as a percentage of pharmaceutical sales was 14.4% in 1990, 14.8% in 1989 and 13.6% in 1988.

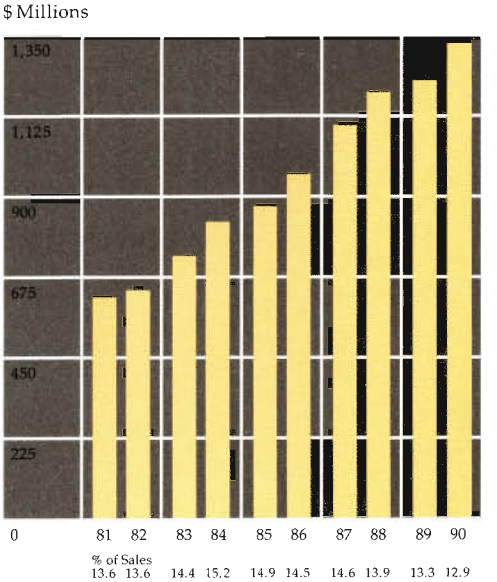
Industry Segments

In 1990, sales in the company's largest segment, the **Pharmaceutical Products Segment**, increased 18%

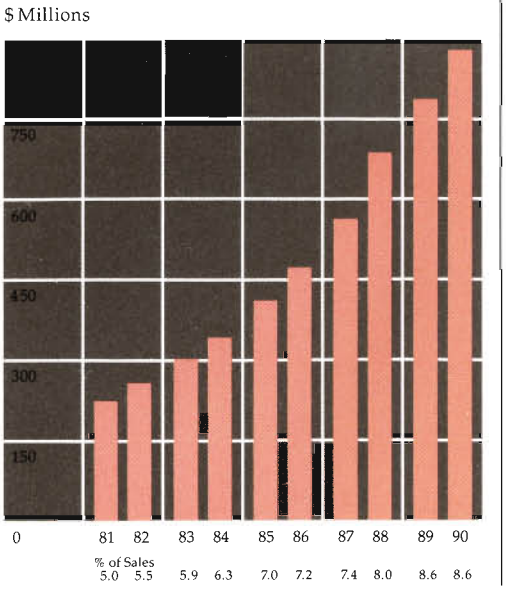
Marketing, Selling and Administrative Expenses



Advertising and Product Promotion Expenses



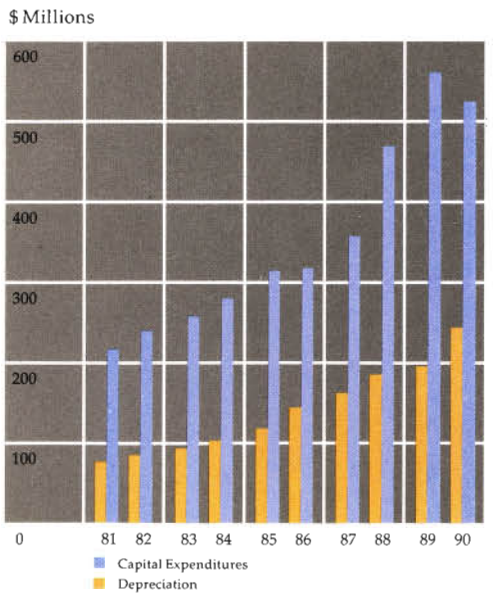
Research and Development Expenses



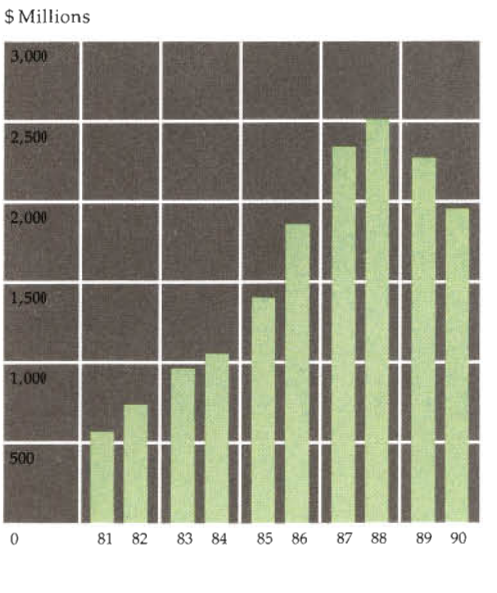
over the prior year. Domestic sales increased 12%, while international sales increased 26%. The worldwide sales increase resulted from an 11% increase in volume, a 4% increase in pricing and a 3% increase due to favorable foreign currency translation. Worldwide sales of cardiovascular drugs, the largest product group in the segment, increased 17% to $2.0 billion, primarily as a result of increased captopril sales. Sales of captopril, sold primarily under the major trademark *Capoten*, increased 19% in 1990 to $1.5 billion. Captopril, an angiotensin converting enzyme (ACE) inhibitor, is the company's largest selling product. Sales of *Questran*, a cholesterol-reducing agent, increased 8%, reflecting the continued success of *Questran Light*, a more convenient and less caloric form. *Prava* (pravastatin), an HMG Co-A reductase inhibitor and the company's new cholesterol-reducing agent, was introduced internationally in 1990, contributing to the strong volume growth in cardiovascular drugs. Sales in the company's anti-infectives sector increased 10%, reaching $1.2 billion. Sales of *Azactam*, the first commercial monobactam antibiotic, which has been proven to be highly effective against life-threatening, gram-negative bacterial infections, and *Amikin*, a semisynthetic aminoglycoside used for serious hospital-acquired infections, both contributed to this growth. Strong volume growth in cefadroxil, a broad-spectrum oral cephalosporin, sold primarily in the U.S. under the trademark *Duricef*, was achieved as a result of reduced generic competition. A 30% increase in sales of anti-cancer drugs to more than $770 million in 1990 is evidence of the company's leadership position in cancer therapy. The sales increase reflects the continued success of *Paraplatin*, a chemotherapeutic agent used in the treatment of ovarian cancer, and strong volume growth in sales of *VePesid*, the largest selling drug in this group, widely used in the treatment of small cell lung cancer and with expanding use in the treatment of gastric cancer. Central nervous system drugs continued their strong performance with sales growth of 22%. This was led by an increase of 40% in sales of *BuSpar*, the company's unique anti-anxiety agent. Diagnostics sales increased 28% in 1990, primarily due to strong volume growth of *Isovue*, a nonionic imaging agent used in cardiology and radiology.

Pharmaceutical products segment sales increased 11% in 1989. This increase resulted from a 10% increase in volume and a 4% increase in pricing, partially offset by a 3% decrease due to unfavorable foreign currency translation. Growth was primarily due to *Capoten, Questran, Azactam, VePesid, Paraplatin, BuSpar* and *Isovue*. In 1988, sales for the segment increased 18% primarily as a result of growth in cardiovascular, anti-infectives, anti-cancer and central nervous sys-

Capital Expenditures and Depreciation



Cash, Time Deposits and Marketable Securities



tem drugs. Operating profit margin in 1990 was 29.4%, compared to 27.1% in 1989, excluding the 1989 charge of $500 million for integrating pharmaceutical operations, and 23.8% in 1988. The increase in 1990 is primarily due to improved manufacturing efficiencies and favorable product mix.

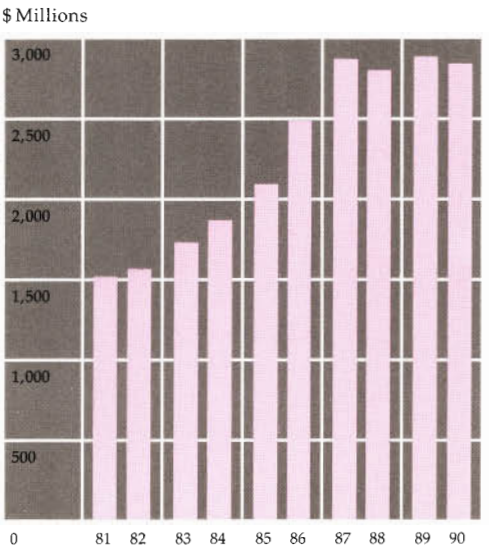
Sales in the **Medical Devices Segment** increased 17% over 1989, reflecting an 11% increase in volume, a 4% increase in pricing and a 2% increase due to the favorable effect of foreign currency translation. Domestic sales increased 12%, while international sales increased 26%. Worldwide sales of prosthetic implants increased 19% led by The *Zimmer Total System*, the most widely used hip replacement products in the world, and the *MGII* Total Knee System. As a result, the company maintained the number one market position in both the hip and knee prostheses markets. Sales of ostomy care products reached $290 million, increasing 27% over the prior year, primarily due to the growth of the *Active Life/Colodress* and the *Sur-Fit/Combihesive* product lines. As a result of continued product enhancements, the company is the worldwide market share leader in ostomy appliances.

Worldwide sales of medical devices increased 11% in 1989 due to a 9% increase in volume and a 4% increase in pricing, partially offset by a 2% decrease due to unfavorable foreign currency translation. Volume increases in 1989, as well as in 1988, were primarily due to growth in the orthopaedic implant and ostomy care businesses. Operating profit margin for the segment was 24.1% in 1990 compared to 24.3% in 1989, excluding the 1989 charge of $16 million for integrating medical devices operations, and 22.3% in 1988.

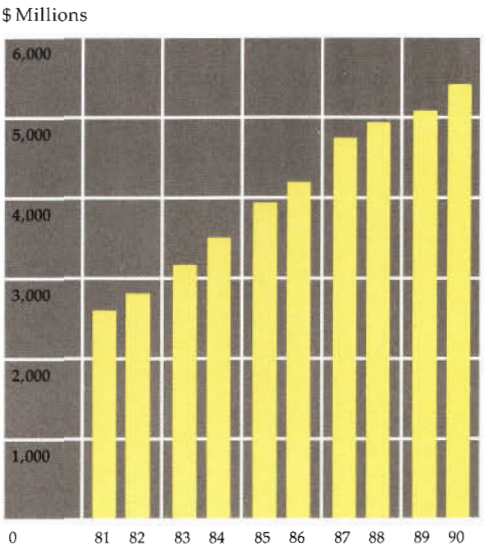
The **Nonprescription Health Products Segment** reported an increase in sales of 7% over 1989, resulting from a 4% increase in selling prices and a 3% increase in volume. Domestic sales increased 4%, while international sales increased 13%. Worldwide sales of nutritional products, the largest product group in this segment, reached $1.2 billion, an increase of 9% over the prior year. International volume gains in the company's principal infant formula, *Enfamil*, contributed to this growth, more than offsetting domestic pricing pressure from the federal government's Women, Infants and Children program. Sales of Gerber Baby Formula, resulting from an agreement entered into with Gerber Products Company in 1989, also contributed to the growth in infant formulas. Sales of the company's adult nutritional products, primarily *Sustagen* and *Isocal*, increased 9%, reflecting the continued international success of these products. Analgesics sales increased 3%, due in part to the success of Aspirin Free *Excedrin*, introduced in 1990.

Worldwide sales of nonprescription health products increased 1% in 1989, primarily due to price

Working Capital



Stockholders' Equity



increases. Strong performances in *Sustagen*, *Isocal* and *Nuprin* offset declines in *Enfamil*, *ProSobee* and *Bufferin*. In 1988, sales growth was due primarily to gains in infant formulas, analgesics and adult nutritionals. Operating profit margin was 22.0% in 1990, 22.3% in 1989, excluding the 1989 charge of $22 million for integrating nonprescription health operations, and 27.0% in 1988.

Sales in the **Toiletries, Beauty Aids and Household Products Segment** decreased by 2% in comparison to the prior year, reflecting a decrease of 5% in volume, primarily due to divestiture of certain businesses in 1990, partially offset by a 2% increase in selling prices and a 1% increase due to favorable foreign currency translation. An increase of 1% in domestic sales was more than offset by a 7% decrease in international sales, primarily due to divestiture of certain businesses. Sales of haircoloring products increased 6%, led by continued growth in *Nice 'n Easy*, *Ultress*, *Miss Clairol* and *Loving Care*. Sales growth in *Windex* glass cleaner and *Renuzit* air fresheners increased 7% and 4%, respectively, in 1990.

In 1989, sales in the toiletries, beauty aids and household products segment were 1% higher than in 1988 as a 4% increase in pricing more than offset a 2% decrease in volume and a 1% decrease due to unfavorable foreign currency translation. Sales growth resulted from increases in haircoloring products, primarily *Miss Clairol* and *Ultress*, anti-perspirants, primarily *Ban*, and household products, primarily *Renuzit Freshell* and *VANiSH*. In 1988, increases in sales of haircoloring products, glass cleaners, air fresheners and bowl cleaners contributed to growth in the segment. Operating profit margin in 1990 increased to 17.8% from 17.4% in 1989, excluding the 1989 charge of $108 million for integrating the company's toiletries, beauty aids and household products operations, and 16.5% in 1988.

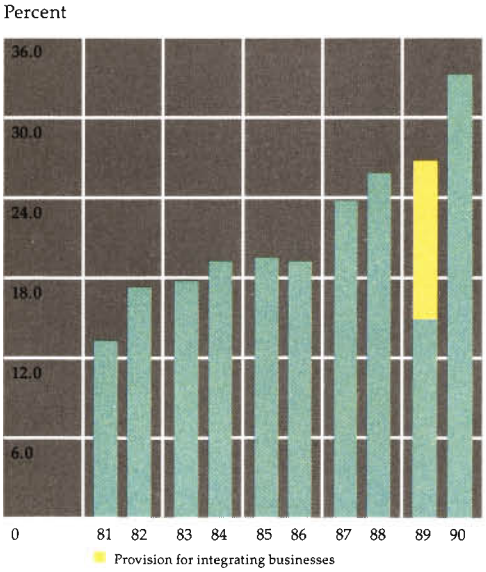
Geographic Areas

Sales of the company's domestic operations increased 7% in 1990 and 1989 compared to 8% in 1988, primarily due to strong volume growth in the company's pharmaceutical and medical devices segments.

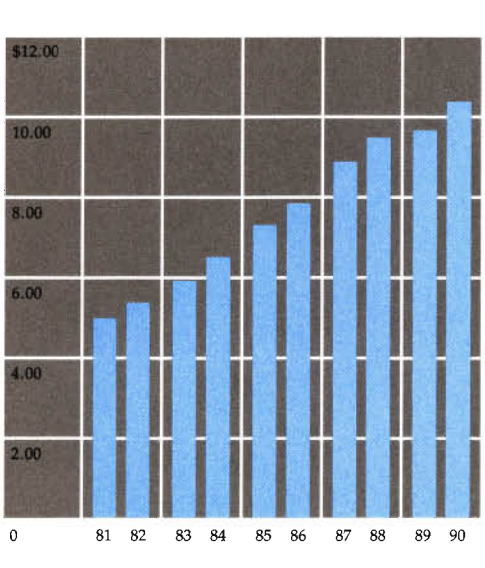
Internationally, the company achieved a 20% increase in 1990, following an 8% increase in 1989 and a 24% increase in 1988.

Sales in Europe, Mid-East and Africa, net of inter-area sales, increased 27%, primarily due to strong volume growth in the company's pharmaceutical products and medical devices segments. Operating profit margin was increased to 23.6% compared to 20.5% in 1989, excluding the 1989 charge of $208 million for integrating operations, due to strong sales performance. Sales in Other Western Hemisphere countries increased 18% due to increases in sales of

Return on Equity



Book Value per Common Share



pharmaceutical and nonprescription health products. In 1990, operating profit margin increased to 21.9% from 21.6% in 1989, excluding the 1989 charge of $47 million for integrating operations. Sales in the Pacific area rose 6% primarily attributed to sales of nonprescription health products. Operating profit margin was 9.6% compared to 10.3% in 1989, excluding the 1989 charge of $41 million for integrating operations.

In 1989, sales in Europe, Mid-East and Africa increased 8%, due primarily to growth in the company's pharmaceutical products and medical devices segments. Operating profits were $436 million, excluding the 1989 charge for integrating operations, compared to $372 million in 1988. Sales in Other Western Hemisphere countries increased 15% attributed to pharmaceutical and nonprescription health products. Operating profits were $166 million, excluding the 1989 charge for integrating operations, compared to $130 million in 1988. In the Pacific area, sales rose 1% due to increases in sales of nonprescription health products primarily in Asia. In 1989, operating profit margin increased to $81 million, excluding the 1989 charge for integrating operations, compared to $71 million in 1988.

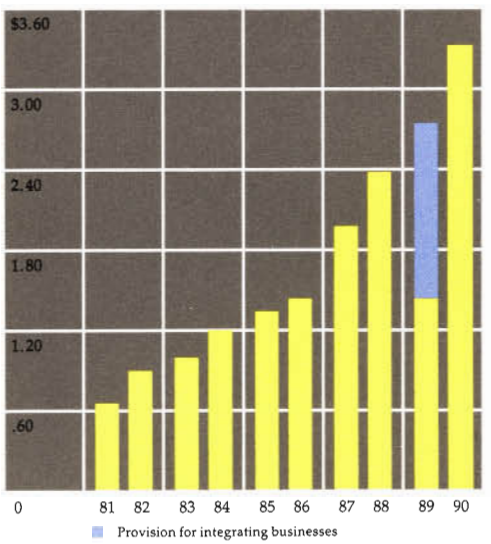
Financial Position

The company maintained its strong financial position as cash, including cash equivalents, time deposits and marketable securities totalled $2.0 billion at December 31, 1990 compared to $2.3 billion and $2.5 billion at December 31, 1989 and 1988, respectively. The company continues to maintain a high level of working capital with over $2.8 billion at December 31, 1990.

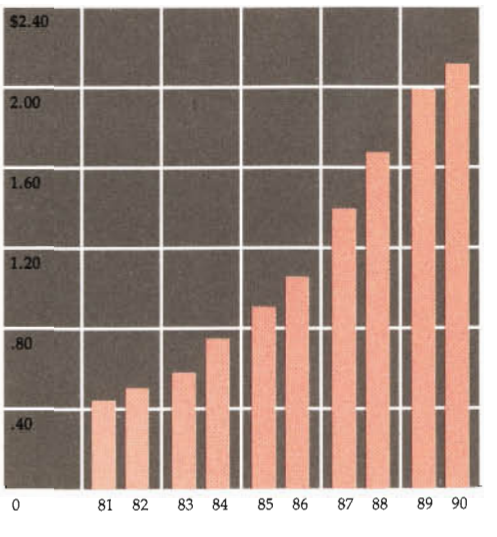
Internally generated funds from operations continue to be the company's primary source for financing expenditures for new plant and equipment. Over the past three years, Bristol-Myers Squibb has invested $1.6 billion in capital expansion in a commitment to maintain superior research facilities and to increase plant efficiency. During this period, the company has also paid $2.5 billion in cash dividends to stockholders, and dividends per common share rose again in 1990 to $2.12, an increase of 6% over the prior year. During the year, 9,507,074 shares of Bristol-Myers Squibb common stock were purchased by the company.

The company's ability to maintain a triple A credit rating, a substantial unused borrowing capacity and a low long-term debt to equity ratio of 4.3% is further evidence of the company's commitment to maintain an overall excellent financial position. Book value per common share at the end of 1990 was $10.34, more than doubling in the last ten years.

Earnings per Common Share



Dividends per Common Share



Quarterly Financial Data (Unaudited)

(in millions of dollars except per share amounts)	*Net Sales*	*Gross Profit*	*Net Earnings*	*Earnings Per Share*
1990:				
First Quarter.....	**$ 2,458**	**$1,758**	**$ 409**	**$.78**
Second Quarter...	**2,484**	**1,788**	**417**	**.79**
Third Quarter....	**2,622**	**1,902**	**496**	**.94**
Fourth Quarter...	**2,736**	**1,978**	**426**	**.81**
Year.....	**$10,300**	**$7,426**	**$1,748**	
1989:				
First Quarter.....	$ 2,265	$1,622	$ 344	$.66
Second Quarter...	2,244	1,605	345	.66
Third Quarter....	2,320	1,646	411	.78
Fourth Quarter*..	2,360	1,660	(353)	(.67)
Year.....	$ 9,189	$6,533	$ 747	

*Included in the fourth quarter of 1989 was a $740 million charge for integrating businesses and a $115 million charge for professional fees and other expenses related to the merger. The after-tax effect of both charges was $693 million, or $1.32 per share.

Market Prices

Bristol-Myers Squibb common and preferred stocks are traded on the New York Stock Exchange and the Pacific Stock Exchange (symbol: BMY). A quarterly summary of the high and low market prices is presented below:

	1990		1989	
	High	*Low*	*High*	*Low*
Common:				
First Quarter.....	**$58¼**	**$50½**	$47½	$44
Second Quarter...	**64⅝**	**51¾**	51¼	46½
Third Quarter....	**65⅞**	**55⅜**	53⅜	46¾
Fourth Quarter...	**68**	**57⅛**	58	49½

	1990		1989	
	High	*Low*	*High*	*Low*
Preferred:				
First Quarter.....	**$236½**	**$229**	$193	$190
Second Quarter ..	**263**	**239**	210	207
Third Quarter....	**254¾**	**254¾**	210	198¾
Fourth Quarter...	**250**	**250**	238	235

Dividends

The company has increased its dividends on common stock in 1990 for the eighteenth consecutive year. Dividend payments per share in 1990 and 1989 were:

	Common		*Preferred*	
	1990	1989	**1990**	1989
First Quarter.....	**$ .53**	$ .50	**$ .50**	$ .50
Second Quarter.....	**.53**	.50	**.50**	.50
Third Quarter	**.53**	.50	**.50**	.50
Fourth Quarter.....	**.53**	.50	**.50**	.50
Year.....	**$2.12**	$2.00	**$2.00**	$2.00

Consolidated Statements of Earnings and Retained Earnings

	(in millions of dollars except per share amounts)	Year Ended December 31, 1990	1989	1988
Earnings	**Net Sales**	**$10,300**	$9,189	$8,558
	Expenses:			
	Cost of products sold	**2,874**	2,656	2,484
	Marketing, selling and administrative	**2,828**	2,580	2,425
	Advertising and product promotion	**1,328**	1,226	1,191
	Research and development	**881**	789	688
	Provision for integrating businesses	**—**	855	—
	Other	**(135)**	(194)	(119)
		7,776	7,912	6,669
	Earnings Before Income Taxes	**2,524**	1,277	1,889
	Provision for income taxes	**776**	530	635
	Net Earnings	**$ 1,748**	$ 747	$1,254
	Earnings Per Common Share	**$3.33**	$1.43	$2.39
Retained Earnings	**Retained Earnings, January 1**	**$ 4,796**	$5,207	$4,594
	Net earnings	**1,748**	747	1,254
		6,544	5,954	5,848
	Less: Dividends	**1,116**	722	641
	Retirement of treasury shares	**—**	436	—
	Retained Earnings, December 31	**$ 5,428**	$4,796	$5,207

The accompanying notes are an integral part of these financial statements.

Consolidated Balance Sheet

Bristol-Myers Squibb Company

	(in millions of dollars)	December 31, 1990	1989	1988
Assets	**Current Assets:**			
	Cash and cash equivalents	**$ 596**	$ 510	$1,966
	Time deposits	**282**	175	149
	Marketable securities	**1,080**	1,597	397
	Receivables, net of allowances	**1,776**	1,578	1,467
	Inventories	**1,366**	1,139	1,044
	Prepaid expenses	**570**	553	399
	Total Current Assets	**5,670**	5,552	5,422
	Property, Plant and Equipment—net	**2,631**	2,350	2,188
	Other Assets	**722**	371	435
	Excess of cost over net tangible assets received in business acquisitions	**192**	224	228
		$9,215	$8,497	$8,273
Liabilities	**Current Liabilities:**			
	Short-term borrowings	**$ 397**	$ 281	$ 679
	Accounts payable	**530**	475	476
	Accrued expenses	**1,354**	1,414	974
	U.S. and foreign income taxes payable	**540**	489	484
	Total Current Liabilities	**2,821**	2,659	2,613
	Other Liabilities	**745**	517	428
	Long-Term Debt	**231**	237	284
	Total Liabilities	**3,797**	3,413	3,325
Stockholders' Equity	Preferred stock, $2 convertible series: Authorized 10 million shares; issued and outstanding 37,871 in 1990, 65,938 in 1989 and 81,730 in 1988, liquidation value of $50 per share	**—**	—	—
	Common stock, par value of $.10 per share: Authorized 1.5 billion shares; issued 532,603,203 in 1990, 525,775,524 in 1989 and 546,877,104 in 1988	**53**	53	55
	Capital in excess of par value of stock	**504**	396	487
	Cumulative translation adjustments	**(61)**	(149)	(114)
	Retained earnings	**5,428**	4,796	5,207
		5,924	5,096	5,635
	Less cost of treasury stock—8,784,350 common shares in 1990, 437,118 in 1989 and 26,086,073 in 1988	**506**	12	687
	Total Stockholders' Equity	**5,418**	5,084	4,948
		$9,215	$8,497	$8,273

The accompanying notes are an integral part of these financial statements.

Consolidated Statement of Cash Flows

Bristol-Myers Squibb Company

(in millions of dollars)	Year Ended December 31, 1990	1989	1988
Cash Flows From Operating Activities:			
Net earnings	**$1,748**	$ 747	$1,254
Depreciation and amortization	**244**	196	185
Provision for integrating businesses	**—**	855	—
Other operating items	**38**	16	18
Receivables	**(219)**	(211)	(159)
Inventories	**(168)**	(123)	(114)
Prepaid expenses	**(8)**	(162)	(22)
Accounts payable	**72**	38	109
Accrued expenses and income taxes	**(44)**	51	148
Deferred income taxes	**85**	(103)	25
Other assets and liabilities	**4**	(114)	45
Net Cash Provided by Operating Activities	**1,752**	1,190	1,489
Cash Flows From Investing Activities:			
Proceeds from sales of time deposits and marketable securities	**1,733**	7,639	5,083
Purchases of time deposits and marketable securities	**(1,330)**	(8,679)	(4,413)
Additions to fixed assets	**(513)**	(555)	(468)
Other, net	**(54)**	(35)	(29)
Net Cash (Used in) Provided by Investing Activities	**(164)**	(1,630)	173
Cash Flows From Financing Activities:			
Short-term borrowings	**88**	(409)	269
Long-term debt	**(49)**	(23)	(3)
Issuances of common stock under stock plans	**145**	197	63
Purchases of treasury stock	**(562)**	(51)	(487)
Dividends paid	**(1,116)**	(722)	(641)
Net Cash Used in Financing Activities	**(1,494)**	(1,008)	(799)
Effect of Exchange Rates on Cash	**(8)**	(8)	2
Increase (Decrease) in Cash and Cash Equivalents	**86**	(1,456)	865
Cash and Cash Equivalents at Beginning of Year	**510**	1,966	1,101
Cash and Cash Equivalents at End of Year	**$ 596**	$ 510	$1,966

The accompanying notes are an integral part of these financial statements.

Notes to Consolidated Financial Statements

Note 1 Accounting Policies

Basis of Consolidation
The consolidated financial statements include the accounts of Bristol-Myers Squibb Company and all of its subsidiaries.

Cash and Cash Equivalents
Cash and cash equivalents include cash on hand, cash in banks and all highly-liquid investments with a maturity of three months or less at the time of purchase.

Marketable Securities
Marketable securities are stated at cost, which approximates market.

Inventory Valuation
Inventories are generally stated at average cost, not in excess of market.

Property and Depreciation
Expenditures for additions, renewals and betterments are capitalized at cost. Depreciation is generally computed by the straight-line method based on the estimated useful lives of the related assets.

Excess of Cost over Net Tangible Assets
The excess of cost over net tangible assets received in business acquisitions subsequent to October 31, 1970 is being amortized on a straight-line basis over periods not exceeding forty years.

Earnings Per Share
Earnings per common share are computed using the weighted average number of shares outstanding during the year. The effect of shares issuable under stock options and warrants is not significant.

Note 2 Business Combination

On October 4, 1989, Squibb Corporation merged with a subsidiary of Bristol-Myers Company, and Bristol-Myers Company changed its name to Bristol-Myers Squibb Company. As a result, 97.4 million shares of Squibb common stock became entitled to be exchanged at a ratio of one share of Squibb for 2.4 Bristol-Myers Squibb shares, and 9.8 million shares of Squibb common stock owned by Squibb as treasury stock were retired. The merger has been accounted for as a pooling-of-interests.

Note 3 Provision for Integrating Businesses

In the fourth quarter of 1989, a charge of $740 million was recorded in connection with the company's plans to integrate the operations of Bristol-Myers and Squibb and to organize its pharmaceutical, medical device, nonprescription health and toiletries, beauty aids and household businesses on a global basis. This charge included the costs of reducing the number of production facilities and employment levels worldwide, employee relocations and other related items. The fourth quarter of 1989 also included an additional $115 million charge for the costs of professional fees and other expenses related to the merger. The after-tax effect of both charges was $693 million, or $1.32 per share.

Note 4 Foreign Currency Translation

Cumulative translation adjustments which represent the effect of translating assets and liabilities of the company's non-U.S. entities, except those in highly inflationary economies, were:

(in millions of dollars)	**1990**	1989	1988
Balance, January 1	**$149**	$114	$116
Effect of balance sheet translations:			
Amount	**(81)**	33	(2)
Tax effect	**(7)**	2	—
Balance, December 31	**$ 61**	$149	$114

Losses resulting from foreign currency transactions and translation adjustments, primarily related to non-U.S. entities operating in highly inflationary economies, principally Brazil, of $74 million, $40 million and $34 million, net of applicable income taxes, are reflected in net earnings for 1990, 1989 and 1988, respectively.

Note 5 Other Income and Expenses

Year Ended December 31, (in millions of dollars)	**1990**	1989	1988
Interest income	**$209**	$233	$209
Interest expense	**(57)**	(63)	(73)
Other—net	**(17)**	24	(17)
	$135	$194	$119

Interest expense was reduced by interest capitalized on major property, plant and equipment projects by $15 million in 1990, $18 million in 1989 and $8 million in 1988. Cash payments for interest, net of amounts capitalized, were $56 million, $57 million and $76 million for 1990, 1989 and 1988, respectively.

Note 6 Inventories

December 31, (in millions of dollars)	1990	1989	1988
Finished goods	$ 745	$ 612	$ 584
Work in process	243	206	172
Raw and packaging materials	378	321	288
	$1,366	$1,139	$1,044

Note 7 Property, Plant and Equipment

December 31, (in millions of dollars)	1990	1989	1988
Land	$ 148	$ 140	$ 119
Buildings	1,355	1,137	1,079
Machinery, equipment and fixtures	2,312	1,959	1,782
Construction in progress	456	568	366
	4,271	3,804	3,346
Less accumulated depreciation	1,640	1,454	1,158
	$2,631	$2,350	$2,188

Capitalized leases, principally machinery, equipment and fixtures, net of accumulated amortization, were $19 million, $16 million and $19 million in 1990, 1989 and 1988, respectively.

Note 8 Retirement Benefit Plans

The company and certain of its subsidiaries have defined benefit pension plans for regular full-time employees. The principal pension plan is the Bristol-Myers Squibb Retirement Income Plan.

Cost for the company's defined benefit plans includes the following components:

Year Ended December 31, (in millions of dollars)	1990	1989	1988
Service cost—benefits earned during the year	$ 73	$ 66	$ 63
Interest cost on projected benefit obligation	120	109	88
Actual losses (earnings) on plan assets	52	(238)	(126)
Net amortization and deferral	(231)	101	4
Net pension expense	$ 14	$ 38	$ 29

The weighted average actuarial assumptions for the company's pension plans are as follows:

December 31,	1990	1989	1988
Discount rate	9.1%	8.8%	9.3%
Compensation increase	5.0%	5.0%	5.3%
Long-term rate of return	12.0%	10.8%	10.9%

The funded status of the plans is as follows:

December 31, (in millions of dollars)	1990	1989	1988
Actuarial present value of accumulated benefit obligations:			
Vested	$(1,033)	$(1,023)	$ (774)
Non-vested	(115)	(74)	(69)
	$(1,148)	$(1,097)	$ (843)
Total projected benefit obligation	$(1,453)	$(1,407)	$(1,071)
Plan assets at fair value	1,381	1,511	1,167
Plan assets (less than) in excess of projected benefit obligation	(72)	104	96
Unamortized net assets at adoption	(160)	(172)	(175)
Unrecognized prior service cost	106	108	99
Unrecognized net gains (losses) for year	161	(12)	8
Prepaid pension cost	$ 35	$ 28	$ 28

Plan benefits are based primarily on years of credited service and on participant's compensation. Plan assets consist principally of equity securities, fixed income securities and group annuity contracts.

The company provides medical and life insurance benefits for certain retired employees who reach normal retirement age while working for the company. The cost of retiree health care and life insurance benefits is expensed as paid and totalled $14 million, $12 million and $10 million in 1990, 1989 and 1988, respectively.

Note 9 Stockholders' Equity

Changes in capital shares and capital in excess of par value of stock were:

	Shares of Common Stock		*Capital in Excess of Par Value of Stock* (in millions of dollars)
	Issued	Treasury	
Balance, January 1, 1988	545,096,569	10,183,283	$455
Exercise of options, rights and warrants	1,721,075	(1,238,376)	32
Conversions of preferred stock	59,460	—	—
Purchases	—	17,141,166	—
Balance, December 31, 1988	546,877,104	26,086,073	487
Issued pursuant to stock plans, options, rights and warrants	2,399,390	(3,641,109)	84
Conversions of preferred stock	66,826	—	—
Purchases	—	1,559,950	—
Retirements	(23,567,796)	(23,567,796)	(175)
Balance, December 31, 1989	525,775,524	437,118	396
Issued pursuant to stock plans, options, rights and warrants	3,259,744	(1,159,842)	77
Conversions of preferred stock	118,581	—	—
Purchases	—	9,507,074	—
Business acquisition	3,449,354	—	31
Balance, December 31, 1990	532,603,203	8,784,350	$504

On October 3, 1989, the stockholders approved an increase in the authorized shares of common stock from 750 million to 1.5 billion shares.

Each share of the company's preferred stock is convertible into 4.24 shares of common stock and is callable at the company's option. The reductions in the number of issued shares of preferred stock in 1990, 1989 and 1988 were due to conversions into common stock.

Dividends paid per common share were $2.12 in 1990, $2.00 in 1989 and $1.68 in 1988.

Under the company's stock option plans, officers, directors and key employees may be granted options to purchase the company's common stock at 100% of the market price on the day the option is granted. Additionally, the plans provide for the granting of stock appreciation rights whereby the grantee may surrender exercisable options and receive common stock and/or cash measured by the excess of the market price of the common stock over the option exercise price.

The company's restricted stock award plan provides for the granting of up to 3,000,000 shares of common stock to key employees, subject to restrictions as to continuous employment except in the case of death or normal retirement. Restrictions generally expire over a five year period from date of grant. At December 31, 1990, a total of 1,690,000 shares were outstanding under the plan.

Stock option transactions were:

	Shares of Common Stock	
	Available for Option	Under Option
Balance, January 1, 1988	30,755,849	18,133,126
Granted	(3,495,225)	3,495,225
Exercised	—	(3,082,314)
Surrendered	—	(430,384)
Lapsed	133,172	(240,341)
Balance, December 31, 1988	27,393,796	17,875,312
Granted	(1,206,380)	1,206,380
Exercised	—	(4,611,753)
Surrendered	—	(51,373)
Lapsed	496,072	(558,231)
Retired	(13,560,612)	—
Balance, December 31, 1989	13,122,876	13,860,335
Granted	(3,493,700)	3,493,700
Exercised	—	(4,205,135)
Surrendered	—	(6,958)
Lapsed	521,995	(610,360)
Other	250,000	305,619
Balance, December 31, 1990	10,401,171	12,837,201

At December 31, 1990, there were exercisable options outstanding to purchase 8,391,173 shares of common stock at prices ranging from $6.43 to $53.75 per share. In each of the years ended December 31, 1990, 1989 and 1988, shares of common stock under options were exercised at prices ranging from $5.01 to $53.16.

There were 32,202 warrants at December 31, 1990 to acquire shares of the company's common stock at an exercise price of $18.83 per share, expiring on December 31, 1994.

At December 31, 1990, 28,858,857 shares of common stock were reserved for issuance pursuant to stock plans, options and warrants and conversions of preferred stock.

Attached to each outstanding share of the company's common stock is one Right. The Rights will be exercisable if a person or group acquires beneficial interest of 15% or more of the company's outstanding common stock, or commences a tender or exchange offer for 15% or more of the company's outstanding common stock. Each Right will entitle stockholders to buy one one-thousandth of a share of a new series of participating preferred stock of the company at an exercise price of $200. The Rights will expire on December 18, 1997. In the event of certain merger, sale of assets or self-dealing transactions, each Right will then entitle its holder to acquire shares having a value of twice the Right's exercise price. The company may redeem the Rights at $.01 per Right at any time until the 15th day following public announcement that a 15% position has been acquired.

Note 10 Provision for Income Taxes

The components of earnings before income taxes were:

Year Ended December 31, (in millions of dollars)	**1990**	1989	1988
U.S.	**$1,789**	$ 941	$1,263
Non-U.S.	**735**	336	626
	$2,524	$1,277	$1,889

The provision for income taxes consisted of:

Year Ended December 31, (in millions of dollars)	**1990**	1989	1988
Current:			
U.S. Federal	**$381**	$457	$348
Non-U.S.	**266**	236	262
State and local	**75**	61	51
	722	754	661
Deferred:			
U.S.	**66**	(175)	(1)
Non-U.S.	**(12)**	(49)	(25)
	54	(224)	(26)
	$776	$530	$635

The 1989 deferred tax provision resulted from costs to be incurred for integrating operations, which is deductible in later years.

Income taxes paid during the year were $477 million, $612 million and $634 million for 1990, 1989 and 1988, respectively.

The company's provision for income taxes for 1990, 1989 and 1988 was different from the amount computed by applying the statutory United States Federal income tax rate to earnings before income taxes, as a result of the following:

	% of Earnings Before Income Taxes		
	1990	1989	1988
U.S. statutory rate	**34.0%**	34.0%	34.0%
Tax exemptions of operations in Puerto Rico	**(5.3)**	(5.0)	(5.3)
State and local taxes	**2.0**	1.9	1.8
Non-U.S. operations	**.2**	1.3	3.0
Integration and non-deductible merger expenses	**—**	8.9	—
Other	**(.1)**	.4	.1
	30.8%	41.5%	33.6%

Prepaid taxes were $317 million, $332 million and $223 million at December 31, 1990, 1989 and 1988, respectively.

The deferred income tax liability, included in Other Liabilities, was $150 million, $60 million and $165 million at December 31, 1990, 1989 and 1988, respectively.

The company has settled with the Internal Revenue Service its United States Federal income tax returns through 1984.

Research tax credits, of approximately $15 million in 1990, $14 million in 1989 and $13 million in 1988, are reflected as a reduction of income taxes in the year in which credits are allowed for tax purposes.

United States Federal income taxes have not been provided on substantially all of the unremitted earnings of non-U.S. subsidiaries, since it is management's practice and intent to reinvest such earnings in the operations of these subsidiaries. In those instances where it is the intent to remit earnings, United States Federal income taxes have been provided to the extent they are not offset by foreign tax credits. The total amount of the net unremitted earnings of non-U.S. subsidiaries was approximately $1,241 million at December 31, 1990.

Note 11 Financial Instruments

The company is party to certain financial instruments to reduce its exposure to fluctuations in interest rates and foreign currencies. These financial instruments include interest rate protection agreements on investments and foreign exchange contracts. The contract amounts of these instruments were:

December 31, (in millions of dollars)	**1990**	1989	1988
Interest rate protection agreements	**$900**	$850	$700
Foreign exchange contracts	**824**	876	337

At December 31, 1990, the company was party to interest rate protection agreements and foreign exchange contracts maturing from 1991 to 1993.

Note 12 Segment Information

The company's products are reported in four industry segments as follows:

Pharmaceutical Products—prescription medicines, mainly cardiovascular drugs and antibiotics, which comprise about forty percent and twenty-five percent, respectively, of the segment's sales, anti-cancer and central nervous system drugs, diagnostic agents and other pharmaceutical products.

Medical Devices—orthopaedic implants, which comprise about forty percent of the segment's sales, ostomy care and wound management products, surgical instruments and other medical devices.

Nonprescription Health Products—infant formulas and other nutritional products, which comprise about sixty-five percent of the segment's sales, analgesics, vitamins, cough/cold remedies and skin care products.

Toiletries, Beauty Aids and Household Products—haircoloring and hair care preparations, which comprise about forty-five percent of the segment's sales, deodorants and anti-perspirants, beauty appliances, household cleansing and specialty products.

Unallocated expenses consist principally of general administrative expenses and net interest income, and in 1989 include a portion of the charge for integrating operations. Other assets are principally cash and cash equivalents, time deposits and marketable securities. Inter-area sales by geographic area for each of the three years ended December 31, 1990, 1989 and 1988, respectively, were: United States—$741 million, $638 million and $558 million; Europe, Mid-East and Africa—$360 million, $302 million and $306 million; Other Western Hemisphere—$34 million, $30 million and $31 million; and Pacific—$3 million, $4 million and $8 million. These sales are usually billed at or above manufacturing costs.

Net assets relating to operations outside the United States amounted to approximately $1,186 million, $957 million and $1,563 million at December 31, 1990, 1989 and 1988, respectively.

Industry Segments (in millions of dollars)	*Net Sales*			*Profit[a]*			*Year-End Assets*		
	1990	1989	1988	**1990**	1989	1988	**1990**	1989	1988
Pharmaceutical Products	**$ 5,261**	$4,442	$3,987	**$1,548**	$ 703	$ 949	**$3,972**	$3,474	$3,132
Medical Devices	**1,436**	1,227	1,102	**346**	282	246	**906**	817	737
Nonprescription Health Products	**1,773**	1,662	1,638	**390**	349	443	**727**	651	620
Toiletries, Beauty Aids and Household Products	**1,830**	1,858	1,831	**326**	215	303	**686**	710	714
Net sales, operating profit and assets	**$10,300**	$9,189	$8,558	**$2,610**	$1,549	$1,941	**$6,291**	$5,652	$5,203

Geographic Areas (in millions of dollars)	*Net Sales*			*Profit[b]*			*Year-End Assets*		
	1990	1989	1988	**1990**	1989	1988	**1990**	1989	1988
United States	**$ 7,017**	$6,478	$6,013	**$1,747**	$1,259	$1,462	**$4,251**	$3,943	$3,484
Europe, Mid-East and Africa	**2,682**	2,127	1,992	**633**	228	372	**1,590**	1,272	1,172
Other Western Hemisphere	**906**	769	672	**198**	119	130	**382**	336	330
Pacific	**833**	789	784	**80**	40	71	**550**	496	505
Inter-area eliminations	**(1,138)**	(974)	(903)	**(48)**	(97)	(94)	**(482)**	(395)	(288)
Net sales, operating profit and assets	**$10,300**	$9,189	$8,558	**2,610**	1,549	1,941	**6,291**	5,652	5,203
Unallocated expenses and other assets				**(86)**	(272)	(52)	**2,924**	2,845	3,070
Earnings before income taxes and total assets				**$2,524**	$1,277	$1,889	**$9,215**	$8,497	$8,273

Industry Segments (in millions of dollars)	*Capital Expenditures*			*Depreciation*		
	1990	1989	1988	**1990**	1989	1988
Pharmaceutical Products	**$360**	$417	$295	**$144**	$111	$103
Medical Devices	**51**	50	56	**26**	21	16
Nonprescription Health Products	**43**	37	29	**29**	27	26
Toiletries, Beauty Aids and Household Products	**38**	36	37	**31**	25	26
Identifiable industry totals	**492**	540	417	**230**	184	171
Other	**34**	22	54	**14**	12	14
Consolidated totals	**$526**	$562	$471	**$244**	$196	$185

[a]The 1989 operating profit of the company's industry segments includes the charge for integrating businesses as follows: Pharmaceutical Products—$500 million; Medical Devices—$16 million; Nonprescription Health Products—$22 million; and Toiletries, Beauty Aids and Household Products—$108 million.

[b]The 1989 earnings before income taxes include the charge for integrating businesses as follows: United States—$350 million; Europe, Mid-East and Africa—$208 million; Other Western Hemisphere—$47 million; Pacific—$41 million; and unallocated expenses—$209 million.

Note 13 Short-Term Borrowings and Long-Term Debt

Short-term borrowings for the years ended December 31, 1990 and 1989 were due primarily to banks, and in 1988 included $448 million due to holders of commercial paper.

The company has short-term lines of credit with domestic and foreign banks. At December 31, 1990, the unused portions of these lines of credit were approximately $200 million and $523 million, respectively.

The components of long-term debt were:

December 31, (in millions of dollars)	**1990**	1989	1988
5.906% Term Loan, due June 21, 1993	**$ 47**	$ 44	$ 52
6¼% Promissory Notes, due June 4, 1992	**45**	42	49
6⅜% and 6½% Notes, due annually from 1995 to 2004	**30**	30	30
8⅝% Debentures, due 1992 to 1995	**13**	14	15
5.7% Debentures, due June 1, 1992	**2**	4	5
6.1% Adjustable Rate Notes, due December 1, 2023, paid in 1990	**—**	9	25
Capitalized lease obligations, due in varying amounts through 2005	**15**	11	14
Other, due in varying amounts through 2008	**79**	83	94
	$231	$237	$284

Long-term debt at December 31, 1990 was payable:

Years Ending December 31, (in millions of dollars)	
1992	$104
1993	60
1994	13
1995	10
1996	3
1997 and later	41
	$231

On June 20, 1989, the 6¼% Promissory Notes due June 4, 1992 were refinanced from the previous rate of 8⅜%.

Accrued wages included in Accrued Expenses were $179 million in 1990, $177 million in 1989 and $156 million in 1988. Included in Accrued Expenses and Other Liabilities were $143 million and $203 million in 1990 and $307 million and $186 million in 1989, respectively, relating to the charge for integrating businesses.

Note 14 Leases

Minimum rental commitments under all noncancellable operating leases, primarily real estate, in effect at December 31, 1990 were:

Years Ending December 31, (in millions of dollars)	
1991	$110
1992	92
1993	68
1994	59
1995	56
Later years	501
Total minimum payments	886
Less total minimum sublease rentals	146
Net minimum rental commitments	$740

Operating lease rental expense (net of sublease rental income of $17 million in 1990, $18 million in 1989 and $19 million in 1988) was $119 million in 1990, $121 million in 1989 and $112 million in 1988.

Report of Management

Management is responsible for the accompanying consolidated financial statements, which are prepared in accordance with generally accepted accounting principles. In management's opinion, the consolidated financial statements present fairly the company's financial position, results of operations and cash flows. In addition, information and representations included in the company's Annual Report are consistent with the financial statements.

The company maintains a system of internal accounting policies, procedures and controls intended to provide reasonable assurance, at appropriate cost, that transactions are executed in accordance with company authorization, are properly recorded and reported in the financial statements, and that assets are adequately safeguarded. The company's internal auditors continually evaluate the adequacy and effectiveness of this system of internal accounting policies, procedures and controls.

The Audit Committee of the Board of Directors is comprised solely of non-employee directors and is responsible for overseeing and monitoring the quality of the company's accounting and auditing practices. The Audit Committee meets several times during the year with management, the internal auditors and the independent accountants to discuss audit activities, internal controls and financial reporting matters. The internal auditors and the independent accountants have full and free access to the Audit Committee.

The appointment of Price Waterhouse as the company's independent accountants by the Board of Directors was ratified by the stockholders. Price Waterhouse's Report to the Board of Directors and Stockholders of Bristol-Myers Squibb Company appears on this page.

Report of Independent Accountants

To the Board of Directors
and Stockholders of
Bristol-Myers Squibb Company

In our opinion, the accompanying consolidated balance sheet and the related consolidated statements of earnings and retained earnings and of cash flows present fairly, in all material respects, the financial position of Bristol-Myers Squibb Company and its subsidiaries at December 31, 1990, 1989 and 1988, and the results of their operations and their cash flows for the years then ended in conformity with generally accepted accounting principles. These financial statements are the responsibility of the company's management; our responsibility is to express an opinion on these financial statements based on our audits. We conducted our audits of these statements in accordance with generally accepted auditing standards which require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for the opinion expressed above.

153 East 53rd Street
New York, New York 10022

January 17, 1991

Ten-Year Financial Summary

	(in millions of dollars except per share amounts)	1990	1989	1988
Operating Results	Net Sales	**$10,300**	$9,189	$8,558
	Expenses:			
	Cost of products sold	**2,874**	2,656	2,484
	Marketing, selling and administrative	**2,828**	2,580	2,425
	Advertising and product promotion	**1,328**	1,226	1,191
	Research and development	**881**	789	688
	Other*	**(135)**	661	(119)
		7,776	7,912	6,669
	Earnings Before Income Taxes**	**2,524**	1,277	1,889
	Provision for income taxes	**776**	530	635
	Net Earnings**	**$ 1,748**	$ 747	$1,254
	Dividends paid on common and preferred stock	**$ 1,116**	$ 722	$ 641
	Earnings per common share**	**3.33**	1.43	2.39
	Dividends per common share	**2.12**	2.00	1.68
Financial Position at December 31	Current assets	**$ 5,670**	$5,552	$5,422
	Property, plant and equipment—net	**2,631**	2,350	2,188
	Total assets	**9,215**	8,497	8,273
	Current liabilities	**2,821**	2,659	2,613
	Long-term debt	**231**	237	284
	Total liabilities	**3,797**	3,413	3,325
	Stockholders' equity	**5,418**	5,084	4,948
	Average common shares outstanding (in millions)	**525**	523	525
	Book value per common share	**$ 10.34**	$ 9.67	$ 9.49

*Includes provisions for integrating businesses of $855 million in 1989 and $58 million in 1981 and a provision for permanent impairment of certain foreign assets and operations of $68 million in 1986.

** Excludes discontinued operations for 1986 and prior years.

1987	1986	1985	1984	1983	1982	1981
$7,558	$6,620	$5,849	$5,473	$5,126	$4,721	$4,565
2,302	2,081	1,947	1,877	1,843	1,761	1,822
2,126	1,814	1,583	1,478	1,404	1,350	1,275
1,100	962	874	831	736	640	622
563	474	412	344	301	260	226
(161)	49	(137)	(95)	(52)	(63)	36
5,930	5,380	4,679	4,435	4,232	3,948	3,981
1,628	1,240	1,170	1,038	894	773	584
560	455	438	392	357	300	250
$1,068	$ 785	$ 732	$ 646	$ 537	$ 473	$ 334
$ 526	$ 404	$ 342	$ 284	$ 229	$ 203	$ 180
1.98	1.44	1.35	1.20	1.01	.91	.66
1.40	1.06	.90½	.75	.58⅛	.50⅞	.44½
$5,006	$4,264	$3,641	$3,138	$2,929	$2,716	$2,607
1,927	1,716	1,534	1,336	1,201	1,107	1,010
7,514	6,592	6,046	5,269	4,843	4,557	4,320
2,129	1,766	1,541	1,266	1,193	1,148	1,090
279	327	299	297	291	444	493
2,759	2,398	2,093	1,759	1,666	1,736	1,718
4,755	4,194	3,953	3,510	3,177	2,821	2,602
538	543	542	538	530	519	510
$ 8.88	$ 7.84	$ 7.30	$ 6.51	$ 5.93	$ 5.36	$ 5.00

Bristol-Myers Squibb Company
Principal Products

Pharmaceuticals

Cardiovascular Therapy

Capoten
Capozide
Corgard
Corzide
Enkaid
K-Lyte
Klotrix
*Prava**
Questran
Salutensin
*Sotacor**
*Staril**

Cancer Therapy

BiCNU
Blenoxane
CeeNU
Cytoxan
Hydrea
Ifex
Megace
Mutamycin
Paraplatin
Platinol
Rubex
Teslac
VePesid
*Vumon**

Infectious Disease Therapy

Amikin
Azactam
*Bricef**
Duricef
Cefazolin
Cephalexin
Dynapen
Fungizone
Kantrex
Mycostatin
Nafcil
Penicillin G—Sodium
Polymox
Tobramycin
Trimox
Velosef

Central Nervous System Therapy

BuSpar
Desyrel
Prolixin
Stadol

Dermatological Therapy

Exelderm
Halog
Kenalog
Lac-Hydrin
Moisturel
Mycolog II
Mycostatin
Ultravate
Westcort

Diagnostics

CardioGen-82
CardioTec
Choletec
Cystografin
Gastrografin
Isovue
Isovue-M
Kinevac
Oragrafin Calcium Granules
Oragrafin Sodium Capsules
Renografin
Sinografin

Other Pharmaceutical Products

Deladumone
Delatestryl
Delestrogen
Estrace
Mucomyst
Naldecon
Natalins Rx
Ovcon
Quibron

Nutritional Products

Infant Formulas

Enfamil
*Enfalac**
*Enfapro**
Gerber Baby Formula
Metabolic formulas
Nutramigen
Pregestimil
ProSobee

Enteral Nutritionals

Isocal
Specialty formulas
Sustacal

Vitamin Products

Natalins (OTC)
Theragran
Vi-Sol/Vi-Flor pediatric vitamins

Other Nutritional Products

*Boost**
Nutrament
*Sustagen**
Ricelyte

Medical Devices

Orthopaedic Implants

Complete line of spinal fixation systems
ECT Internal Fracture Fixation Systems
Fenlin Total Shoulder System
Free-Lock Compression Hip Fixation System
Herbert Bone Screw System
Insall/Burstein II Modular Total Knee System
Magna Fx Cannulated Screw Fixation Systems
Statak Soft Tissue Attachment System
The *Zimmer Total System* of artificial hips:
Harris/Galante Porous Hip
Zimmer Anatomic Hip
Zimmer Harris Precoat Plus
The *Miller/Galante* artificial knee system:
MG II Porous Total Knee
MG II Precoat Total Knee
Miller/Galante Unicompartmental Knee System

Other Implants

Audiant Implantable Hearing Device
Plastic surgery prostheses
Products for ear, nose and throat/head and neck surgical specialties
Reconstructive and ancillary products
Ureteral stents
Urological prostheses

Ostomy Products

One-piece ostomy pouches, marketed as *Colodress, Active Life, Ileodress, Unidress* and *Urodress*
Little Ones pediatric ostomy products
Stomahesive and *Durahesive* skin barriers
Two-piece ostomy products include *Combihesive, Sur-Fit* System, *Sur-Fit Flexible, Gentle Touch* Postoperative system and Surgicare System 2
Visi Flow and *Sur-Fit* irrigation products

Patient Care and Wound Care Products

ATS 500/1500 Tourniquet Systems
DuoDERM line of wound care products, marketed as *Granuflex* or *Varihesive* in some countries
General hospital products
Knee immobilizers
Meshgraft II Tissue Expansion System
Orahesive Oral Bandage
Patient supports
Pulsavac Wound Debridement Systems
Snyder Hemovac Wound Drainage Systems
Sports medicine/rehabilitative products
Zim-Flex Synthetic Cast Tape
Zimcode Traction Frames and Accessories
Zimmer Air Dermatome Skin Grafting System

Powered Instruments

Hall Micro 100 and *Hall Micro E* Small Bone Powered Surgical Instruments
Hall Neurairtome System—Powered Neurological Compound Drill
Hall Osteon Otology Drill System
Hall Powered Sternum Saws
Hall Series 3 and *Hall Versipower* Large Bone Powered Surgical Instruments
M.P.S. and *Skeeter* Microsurgical Drill Systems
Oral-maxillofacial reconstructive products
Revision surgery instrumentation systems

Arthroscopy Products

Intra-Arc Blades
Intra-Arc Drive System
IntraVision Camera
Shutt Instruments

Microsurgical Products

Hand-held instruments
Instruments for ear, nose and throat surgery
NIM-2 Cranial Motor Nerve Monitor
Specialty products for ophthalmology
Sterile microscope, procedure and equipment drapes for surgery

Other Medical Devices

Angiography disposables
Angiography kits and trays
Critical care catheters
Electrosurgery products
Endoscopy equipment and instruments
Guidewires
Hand-held instruments
Hemoclip Ligation Clips
Hemostatic agents
Office-based urodynamic equipment
Ophthalmic disposables
Sterilization disposables
Ureteroscopes
Visistat Skin Stapler

Consumer Products

Nonprescription Pharmaceuticals

Ammens Medicated Powder
Aspirin Free *Excedrin*
Ban
Bufferin
Colace
Comtrex
Comtrex A/S
Datril
Excedrin
Excedrin P.M.
4-Way
Mum
Naldecon (OTC)
No Doz
Nuprin
Peri-Colace
Sinus Excedrin
Spec-T
Squibb Glycerin Suppositories
Squibb Mineral Oil
Tempra
Therapeutic *Mineral Ice*

Haircoloring and Hair Care Products

Balsam Color
Basic White Powder Lighteners
Beautiful Collection
Body on Tap
Clairesse
Clairmist Hair Sprays
Condition hair care products
Final Net Hair Sprays
*Finalé**
Frost & Tip
Infusium 23 hair care line
Instant Beauty
Jazzing
Kaleidocolors
Logics
Loving Care
Miss Clairol
*Motif**
Nice 'n Easy
Option Instant and Gradual
Quiet Touch Hairpainting
Score hair grooming gel
Second Nature
Torrids
Ultress
Vitalis hair preparation line

Skin Care Products

Alpha Keri
Fostex
Keri Lotion
PreSun
Sea Breeze

Household Products

Behold
Drāno
Endust
Institutional and commercial products
Mr. Muscle
O-Cedar handle goods
Renuzit air fresheners
Scrubbee
Twinkle
Vanish bowl care products
Windex

Personal Care Appliances

Back Fixer back massagers
Beauty Lights makeup mirrors
Body Builder hairstyling brushes
Curl-Technics hairsetter
Foot Chargers foot massagers
Foot Spa
Kindness heated rollers
Lock 'n Roll flexible stylers
Salon Power hairdryers and other turbo and professional dryers
Set-To-Go hairsetter
Style Setter heated rollers
True-To-Light makeup mirrors

*Currently marketed only outside the U.S.

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[2]Committee on Directors and Corporate Governance

[3]Compensation and Management Development Committee

[4]Executive Committee

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800-662-7999 (*VIDEX* Information Center)
Clairol Consumer Hotline
800-223-5800
800-447-7262 (for questions in Spanish)
Clairol Professional Hotline
800-221-4900
ConvaTec-Professional Service
800-422-8811
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800-632-1684
Mead Johnson Nutritionals
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800-345-0248 (*Ricelyte*)
Squibb U.S. Pharmaceuticals
800-332-2056
Surgitek
800-447-8899 (Plastic surgery)
800-558-9494 (Urology and urodynamics)
Westwood-Squibb
800-333-0950
Xomed-Treace
800-874-5797

Annual Meeting of Stockholders
Tuesday, May 7, 1991
9:45 A.M.
Hotel duPont
11th and Market Streets
Wilmington, Delaware 19801

If you would like a copy of the Company's Form 10-K (1990 annual report filed with the Securities and Exchange Commission), you may obtain it without charge by writing to the Secretary,
Bristol-Myers Squibb Company
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New York, New York 10154

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