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Strategy	Research Center	Partner
Identify drugs based on genes associated with obesity and type II diabetes	**Nutley**	**Millennium** : Positional cloning, target identification
Identify drugs based on genes coding for potential pharmaceutical targets		
– Novel antivirals for HBV, HCV, HPV infections	**Welwyn**	None
– Novel antibiotics for Staph. aureus, Strep. pneumoniae infections	**Basel**	**Human Genome Sciences** : Genome sequencing
– All therapeutic categories	**Nutley**	**Incyte** : Human gene sequences, transcript maps, cDNA clones **Synteni** : Gene expression profiling **Jackson Laboratories** : Bioinformatics

Fig. 8. *Genome-based drug discovery at* Roche*: summary*

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In particular, the latter approach will take us into the future of drug discovery. It will be the era of large-scale biological experimentation and the use of computers to analyze biological information, the era of large-scale chemical syntheses and ultrahigh throughput screening. Genes, proteins, targets and leads will no longer be handled one by one but in large numbers. The human genome itself will become a tool in drug discovery.

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Roche Pharma Research from the Past to the Present

Eckart Gwinner* and **Bruno Dalle Carbonare**

This year, on October 1, the Basel firm *F. Hoffmann-La Roche* celebrated its 100th anniversary. During its life span, *Roche* has grown from a small laboratory to a broadly based multinational health-care company that is driven from the beginning by intensive research. Measured by its annual sales, *Roche* is ranking today in the league of the top ten pharmaceutical companies in the world and holds the number one position in the hospital sector. Last year, the *Roche* group invested on Research and Development (R&D) again more than 20% of its pharmaceutical sales of 9.2 billion CHF (prescription drugs and OTC products). These expenditures of 1.96 billion CHF, among the highest in the industry both in absolute and relative terms, have been spent to generate further growth above average (*Table 1*).

The Beginning: A Young Entrepreneur Takes His Chances

With financial assistance from his father, the 28-year-old businessman *Fritz Hoffmann*, just married to *Adèle La Roche*, established 1896 a small pharmaceutical specialties company on the banks of the Rhine River in Basel. At this time, when the Industrial Revolution was changing the face of Europe, migration from rural areas to centers of industry and trade was in full swing, causing city populations to swell and the need of medicines to grow rapidly.

However, a standardized drug therapy in the modern sense did not exist. In those days, most prescriptions had to be compounded individually by pharmacists. The effectiveness and safety of medicines could very considerably depending on the quality of the raw materials used, the skill of the pharmacists and the experience of the prescribing physicians. Pharmacies provided the first synthetic compounds from coal-tar and, of course, preparations like morphine or quinine which had been isolated from plants or plant components. What was lacking, however, was a broad-

**Corresponcence*: Diplomchemiker E. Gwinner
Pharma Research Staff International – Communication
F. Hoffmann-La Roche Ltd.
CH-4070 Basel

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However, a standardized drug therapy in the modern sense did not exist. In those days, most prescriptions had to be compounded individually by pharmacists. The effectiveness and safety of medicines could very considerably depending on the quality of the raw materials used, the skill of the pharmacists and the experience of the prescribing physicians. Pharmacies provided the first synthetic compounds from coal-tar and, of course, preparations like morphine or quinine which had been isolated from plants or plant components. What was lacking, however, was a broad-

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CH-4070 Basel

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ly based industrial supply of drug substances and formulations of constant quality.

Fritz Hoffmann founded the company because he saw the great scientific and economic changes of his time as a chance to take advantage of the rapid evolution of drug therapy. His goal: to develop and to manufacture novel drugs of uniform strength and quality and to market them globally by combining developments in industrial technologies with a vision of establishing international scientific and commercial links.

First Successes

The initial research of the new company was focused by the pharmacist *Carl Schaerges*, the first head of R&D, on thyroid-gland activity. This resulted 1896 in the first patent and scientific publications and in *Aiodin*®, the earliest in a series of thyroid preparations (see *Table 2*).

Fritz Hoffmann also recognized very early the value of international product labels and began to use his wife's maiden name '*Roche*' for the product trademark of the most successful product *Sirolin*®, a nonprescription cough syrup with orange flavor and *Roche*'s own *Thiacol*® (potassium-guaiacol sulfonate) as its ingredient. (A cough syrup with the *Sirolin*® label is registered and sold on the French market furthermore today.)

Roche started from the beginning with an international strategy: The production facilities were located 1897 in Grenzach, Germany, very near to Basel and further affiliates have been founded in Italy (1897), France (1903), USA and Brazil (1905), Spain (1906), Austria (1907), Great Britain (1908) and Russia (1910).

At the turn of this century, extracting the active components of medicinal plants was an important branch of early industrial drug manufacture. *Roche* centered its work mainly on the digitalis glycosides and the alkaloids of ergot and opium. Scientists and engineers in Grenzach developed a so-called double extraction method which was significantly more efficient than earlier processes and was therefore kept as a secret for many years to stay ahead of the competition.

Productive Collaborations with Academia

In this time, *Max Cloëtta* (1868–1940), the first Swiss professor of pharmacology, had begun to work on the active glyco-

Table 1. *Continuous Commitment to R&D.* R&D Spending of the top ten pharmaceutical companies in 1995.

	Sales	R&D Spend	R&D as % Sale
Glaxo/Wellcome	12518	1884	15.1
Merck&Co	11314	1331	11.8
Hoechst/Marion	8420	1250	14.8
Novartis (Ciba/Sandoz)	8115	1695	20.9
BristolMyersSquibb	7410	1007	13.6
Pfizer	7072	1295	18.3
Roche	6658	1664	24.9
Johnson&Johnson	6274	770	12.3
AmericanHome	6074	1220	20.1
SmithKline Beecham	6056	894	14.8
***Roche* Ranking**	**7**	**3**	**1**

Source: Lehman Brothers 1996; figures are in USD and relate to prescription pharmaceuticals only.

Table 2. *Major Breakthroughs in the Past 100 Years and Recent Launches*

1896	*Aiodin*	Prevention of goitre
1904	*Digalen*	Cardiovascular diseases
1909	*Pantopon*	Pain, colic, spasm, cough and anxiety
1923	*Iloglandol*	Diabetes
1931	*Prostigmin*	Muscle spasm, intestinal immotility
1934	*Redoxon*	Prevention of scurvy
1949	*Gantrisin*	Bacterial infections
1952	*Rimifon*	Tuberculosis
1953	*Marcoumar*	Blood coagulation
1960/63	*Librium/Valium*	Sedation, psychosomatic disorders
1962	*Fluoro-uracil*	Cancer
1969	*Bactrim*	Bacterial infections
1970/73	*Larodopa/Madopar*	*Parkinson*'s disease
1974	*Fansidar*	Malaria
1982	*Tigason/Roaccutan*	Psoriasis/Severe acne
1982	*Rocephin*	Severe bacterial infections
1986	*Roferon-A*	Hairy-cell leukemia, *Kaposi* sarcoma
1990	*Aurorix*	Depression
1991	*Neupogen*	Neutropenia
1991	*Loceryl*	Fungal infections
1992	*Quinodis*	Bacterial infections
1992	*Globocef*	Bacterial infections
1992	*Hivid*	Aids
1993	*Pulmozyme*	Cystic Fibrosis
1994	*Vesanoid*	Cancer
1995	*Invirase*	Aids

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sides of the purple foxglove at the University of Zurich. The chemist *Emil Christoph Barell*, the most important partner of *Fritz Hoffmann* in the young company (and the powerful chief executive of *Roche* over a period of 32 years after *Hoffmann*'s early death in 1920), initiated 1901 a close collaboration with *Cloëtta* which was very productive for nearly 40 years. *Cloëtta* developed a standardized mixture of the pure cardiac digitalis glycosides as a injectable drug which was launched successfully 1904 under the trademark *Digalen*®. This product proved to be exactly what the medical profession has been looking for and remained on the market until 1964 (see *Table 3*).

A similar collaboration with *Hermann Sahli* (1856–1933), professor of medicine at the University of Bern, resulted 1906 in the analgesic *Pantopon*® which contains a combination of all opium alkaloids for the treatment of severe pain, spasms, colics and is still on the market.

In 1910, the biochemist *Markus Guggenheim* (1885–1970) was appointed to the head of pharmacology and then put in charge of research, which has been directorless since the death of *Carl Schaerges* in 1907. *Guggenheim* built up a strong interdisciplinary research group and a worldwide network of personal contacts to academia. His interest was focused until his retirement in 1947 on natural biologically active compounds, particularly on hormones, vitamins and some amines and amino acids as levodopa.

Table 3. *Major Collaborations with Universities in the Past and Some Recent Research Collaborations with Academic Institutions*

1901	University of Zurich (Prof. *M. Cloëtta*)	Cardiac glycosides (*Digalen*)
1906	University of Berne (Prof. *H. Sali*)	Pain, anaesthesia (*Pantopon*)
1926	University of Edinburgh (Prof. *G. Brager*)	Beri-Beri (Vitamin B_1), Thyroid hormones (*Thyroxin*), intestinal stimulants (*Prostigmin*)
1935	University of Zurich (Prof. *P. Karrer*)	Riboflavin (Vit B_2), Vit A
1949	Universitiy of Innsbruck (Prof. *H. Bretschneider*)	Antibiotics (*Madribon, Gantanol, Fanasil etc.*), Depression (*Marsilid, Marplan*)
1952	University of Chicago (Prof. *Zeller*)	Depression (*Marsilid, Marplan*)
1956	University of Wisconsin (Prof. *C. Heidelberger*)	Cancer (*5-Fluoro-uracil*)
1961	Universitiy of Vienna (Prof. *W. Birkmayer*)	Parkinson (*Larodopa, Madopar*)
1992	Washington University, St. Louis	Neurobiology
1994	University of Washington, Seattle	Cardiovascular research
1994	Taiwan University, Taipei	Screening for new compounds
1995	Jackson Laboratory, Bar Harbor	Bioinformatics
1996	Institute of Microbiology, Beijing	Analgesia, lower urinary tract disorders
1996	Shanghai Institute of Organic Chemistry	Neurobiology
1996	University College, London	Neuropharmacology

The Age of Vitamin Research

Since the mid of the twenties, several prominent European biochemists started to investigate the group of vitamins. But it was the young, highly talented chemist *Tadeusz Reichstein* (1897–1996) at the Institute of *Leopold Ruzicka* in Zurich, who has found an effective synthesis of vitamin C (ascorbic acid) in 1933. He offered his method to *Roche* and *Guggenheim* accepted. *Franz Elger* scaled up the process and the first fifty kilograms of vitamin C had been produced in 1934. The basic principle of *Reichstein*'s method is still in use. This marks the real start of vitamin manufacturing at *Roche*. In the same year, *Redoxon*®, the first vitamin medication, was launched.

Two years later, the elegant synthesis of vitamin B_1 by *Alexander Todd* and coworkers in England enabled *Roche* to start up production quickly. Simultaneously, the riboflavin (vitamin B_2) synthesis of *Paul Karrer* at Zurich was brought to technical application. Working with *Karrer* and *Todd*, the chemist *Otto Isler* (1910–1992), who joined *Roche* in 1936 after his doctorate by *Ruzicka* in Zürich, synthesized vitamin E in 1938. This vitamin was introduced under the trade name *Ephynal Roche*®, primarily for use in premature newborns.

Isler and coworkers developed then 1947 in a pioneering work the first industrial synthesis of vitamin A and opened the way to manufacturing a wide range of other products including carotinoids and retinoids. The latter play since 1982 an important role in the dermatological prescription drugs *Roaccutan*® and *Tigason*®/*Neotigason*®.

It should be mentioned that in the first ten to fifteen years, vitamin research was focused on the development of real drugs to treat severe vitamin deficiencies, phenomena which have mostly disappeared in the industrialized today but are evident further in many third-world countries.

The Era of Chemotherapy...

In the forties, *Roche* started a broad drug discovery program in the field of infectiology. The antibacterial drug *Grantrisin*®, a highly water-soluble sulfonamide for the treatment of uninary tract infections, was the first result and launched in 1949; it is still widely used in several countries.

In this time, *Roche* had 113 scientists working in research: 55 in Basel, 50 in Nutley, USA, and 8 in Welwyn, England.

A real breakthrough in the battle against tuberculosis was the discovery and development of isoniazide which was launched worldwide under the name *Rimifon*® in 1952. (The New York Post put on the front page the headline 'Wonder Drug Fights TB'.)

A further milestone in the field of antibacterial chemotherapy is the combination drug *Bactrim*® which was developed in 1973 as a result of a collaboration between scientists at *Roche* Nutley and the British company *Wellcome*. The combination of two active compound blocks specifically two steps in the bacterial synthesis of folic acid and stops therefore the bacterial growth. *Bactrim*® conserved over the last twenty years its role as a potent antibacterial for respiratory, urinary tract and other bacterial infections. Today, the drug is a highly effective medication against one of the most frequent opportunistic infections in AIDS patients, too.

In the second half of the seventies, *Roche* scientists in Basel synthesized ceftriaxone, a cephalosporine compound with an interesting pharmacological profile: this substance has powerful antibacterial effects on most gram-positive and gram-negative pathogens, especially in life-threatening infections including bacterial meningitis; its specific is the extremely long elimination half-life time and therefore long duration of action. The drug *Rocephin*®, introduced in 1982, has become the number-one product in its class worldwide and the best-seller of the *Roche* Group.

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Today, in collaboration with the US Biotech company *Human Genome Sciences*, the research department of bacterial infectiology in Basel uses the latest methods in the search for genes in the bacterial genomes of *staphylococcus aureus* and *streptococcus pneumoniae* to identify new pharmaceutical drug targets and to develop novel antibiotics.

... and of Neuroactive Drugs

The antituberculosis compound isoniazide was a milestone in the history of drug discovery for another reason as well: clinicians observed an unexpected mood-elevating effect. In the fifties and sixties, these observations gave the lead for the search and discovery of the first monoamino-oxidase inhibitors as antidepressants at *Roche* Nutley (in collaboration with the University of Chicago).

It was in 1957 when the chemist *Leo Sternbach* in Nutley, USA, returning to a group of compounds he had worked on earlier, synthesized some substances leading to a revolutionary class of psychotropic medicines called benzodiazepines. The first of these drugs, shown by the pharmacologist *Lowell Randall* to possess an exciting pattern of muscle relaxing and sedating properties in animal models, was launched as *Librium*® in 1960.

Three years later, *Valium Roche*®, discovered by *Sternbach* too, was introduced into the markets and developed to a spectacular therapeutic and commercial success. The systematic synthesis of benzodiazepine analogues produced further important drugs for the treatment of epilepsy, sleep disorders, anxiety and in anesthesia.

To know that a drug works is important, but to know how and where the drug works, very often opens new avenues in the pharmaceutical research: The first isolation and characterization of the benzodiazepine receptor in the GABA system of the brain in 1977 by a team of scientists in *Roche* Basel (and simultaneously by a Danish group) was such a breakthrough in modern neurobiology. In the eighties, this was followed by the development and introduction into the markets of two further innovative drugs, namely *Dormicum*® (anesthetic, hypnotic) and *Anexate*®, the first benzodiazepine antagonist.

Also during this period, new screening systems were established by a team in the Basel research center. These efforts resulted in the discovery of the first specific, reversible inhibitor of the monoamino-oxidase A (MAO-A), moclobemide, with a unique chemical structure. The drug *Aurorix*® was then introduced in 1990 as an antidepressant with a significant pharmacological profile of high tolerability and good efficacy. In several broad clinical studies, this 'gentle' drug has now also shown good results in social phobia; internationally, it is in the process of registration for the further indication of this psychiatric disorder.

Milestones in the Treatment of *Parkinson*'s Disease

A breakthrough in the field of neurobiological disorders stood out against the skyline in the sixties when *Walther Birkmayer et al.*, in Vienna and *Roche* scientists in Basel began to test the use of levodopa, the natural precursor of the neurotransmitter dopamine, as a substitution therapy in patients with *Parkinson*'s disease: The drugs *Larodopa*® (introduced 1970) and especially *Madopar*® (introduced 1973) were the result of this pioneering research. The dramatic improvement of the quality of life for *Parkinson*'s patients led in 1974 to the award of the French Prix Galien for *Madopar*®. (In the meantime, five other *Roche* drugs received further Prix Galien awards, making *Roche* a leader in this league of innovative pharmaceutical companies.)

During the last years, the classical *Roche* drug *Madopar*®, a combination of levodopa and the dopa-decarboxylase (or DDC) inhibitor benserazide, has received some galenical refinements in order to specifically improve the onset of action and therefore the daily life of patients with *Parkinson*'s disease. However, this standard therapy suffered some drawbacks: An important one is the short half-life of levodopa and the consequent fluctuations of its plasma levels. Partially responsible for the rapid metabolism of levodopa is its massive conversion in the peripheral system to 3-*O*-methyldopa (3-OMD) through the enzyme catechol-*O*-methyltransferase (or COMT). 3-OMD, although not toxic, accumulates in the body due to its longer half-life and can interfere with the transport of levodopa into the brain parenchyma.

It is quite clear that an increased penetration of levodopa as an intact amino acid into the brain would require simultaneous inhibition of the two enzymes primarily involved in the peripheral metabolism of levodopa, namely DDC and COMT. Human erythrocytes also contain COMT; they are easily obtained and can therefore be used for assessing and monitoring the COMT inhibitory effect of drug candidates in screening and also in clinical trials. In contrast, the COMT activity in CNS is much lower than that measured in peripheral organs. The search over several years for a novel orally active COMT inhibitor culminated ten years ago in the Basel laboratories with the identification of RO 40-7592. This compound was then developed to the highly specific and potent drug Tasmar™ (tolcapone) which is at present internationally filed for registration (*Table 4*).

This example demonstrates very clearly the persistance that is required in pharmaceutical research today when tackling unsatisfyingly solved medical problems and working on decisive parts of a puzzle until a complete therapeutic concept emerges. The novel combination of *Madopar*® and Tasmar™ is a more effective and better tolerated treatment of *Parkinson*'s disease with significant life improvement day and night for the patients.

Neuroscience – a Cornerstone of *Roche* Research

Acute or neurodegenerative diseases as ischemic or hemorrhagic stroke or multiple sclerosis and *Alzheimer*'s disease will present the greatest challenges in the next decade. *Roche* is tackling these unmet medical needs by a broad research effort including basic research and strong collaborations with universities and with *Genentech*, the biotechnology pioneer in California, in which *Roche* has hold the majority of shares since 1990. In close cooperation with specialists at the Washington University in St. Louis, USA, several drug discovery programs are under way in Basel in the field of stroke.

In the meantime, an innovative treatment procedure for ischemic strokes has been developed in the US by *Genentech* with the application of *Activase*® (t-PA, a fibrinolytic to treat myocard infarctions) under specific conditions after careful diagnostic evaluation; this procedure has been approved recently by the American Food and Drug Administration.

In the field of *Alzheimer*'s disease, several teams in preclinical research in Basel are working on different concepts to decipher the disease's mechanisms on the cellular and molecular level. But to find a real drug target does not seem to be just next door. In the meantime, lazabemide, a selective inhibitor of monoamino-oxidase B (MAO-B), is undergoing some further clinical evaluations because MAO-B is one of the few enzymes found at increased levels in the brain of *Alzheimer* patients.

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Established Anticoagulants and Novel Cardiovascular Drugs

Starting with organ extracts, scientists at *Roche Basel* developed a heparin anticoagulant in 1938. Launched as *Liquemin*®, it was the first broadly used product in a line of anticoagulants and antihemorrhagics of *Roche*: 1953 followed *Marcoumar*® and the vitamin K preparation *Konakion*®, both standard medications in their therapeutic fields.

Heavy investments in the Basel cardiovascular research over the last ten to fifteen years have resulted in the development of novel drugs: Mibefradil, the first calcium antagonist which specifically addresses the new found T channel in the heart-muscle cells is outstanding in its pharmacological profile. It will be introduced in 1997 under the trademark Posicor™ for the treatment of hypertension, angina pectoris and congestive heart failure. Highly specific platelet aggregation inhibitors (injectable and oral form) are in late clinical development, and the innovative endothelin antagonist bosentan has entered broad clinical testing (*Table 5*).

Since obesity and diabetes have been recognised as main risk factors for cardiovascular diseases, *Roche* has started a broad discovery research program on the genetic basis of this metabolic disease, as well as of arteriosclerosis and stroke, to identify novel drug targets for the causal treatment of these diseases.

A first medication for obese patients was discovered in the eighties: orlistat with the future tradename Xenical™ inhibits pancreas lipases, therefore the fat metabolism in the gut and ultimately the resorption of fat molecules in the food. This drug with its unique mechanism of action in connection with a light diet has shown very promising long-term effects.

Table 4. *Major Development Compounds*

Obesity	Xenical™
Diabetes	IGF-1
Osteoporosis	*Rocaltrol*®, PHRP
Parkinson's disease	Tasmar™
Hypertension, Angina pectoris	Posicor™
Transplantation	*Cellcept*®, Zenapax™
Alzheimer's disease	Lazabemide
Sepsis	Tenefuse
Congestive heart failure	Posicor™, Bosentan
Hepatitis C	IL-12
Thrombosis	Platelet-aggregation inhibitors
Cancer	NeoFurtulon, anti-CD-20-Mab, IL-12
Rheumatoid arthritis (RA)	*Cellcept*®, Tenefuse, cartilage protective agent

Table 5. *Major Research Programs*

Alzheimer's disease	Prevention of senile plaque formation in the brain
Stroke	Prevention of neuronal cell death after stroke
Depression	Increase of serotonin
Congestive heart failure	Antagonize endothelin as a vasoconstrictor
Thrombosis	Inhibitors of TF-Factor VII complex
Inflammation (MS, RA, Psoriasis, Transplantation)	Prevention of cell adhesion, inhibition of T-cell activation and of extracellular matrix degradation
Obesity	Ob-receptor pathway
Diabetes	Modulation of specific pancreatic enzymes
Bacterial infections	New antibiotics, host defense regulation
Viral infections	Antisense, inhibition of viral proteinases
Fungal infections	Inhibition of different fungal enzymes
Cancer	Modulation of cell differentiation, cell cycle and oncogenes

Cancer, Immunology and Viral Infections – a Domain of Biotechnology

In 1968, *Sidney Pestka* started to investigate the alpha interferons at the former *Roche Institute of Molecular Biology* in Nutley. His pioneering research led to a joint project of *Roche* with the biotech company *Genentech* in San Francisco in 1978 to produce the genetically engineered interferon alpha 2a. This was approved in 1986 and launched as the first biotech drug of *Roche* under the name *Roferon*®*-A* for the treatment of hairy-cell leukemia and AIDS-related *Kaposi*'s sarcoma. Today, this interferon is the drug of choice in hepatitis C and B as well as in several cancers therapies.

As a pioneer in the field of genetic engineering, *Roche* developed and introduced two further recombinant drugs: *Neupogen*® (discovered by *Amgen* in California) for the treatment of neutropenias after chemotherapy in cancer patients and *Pulmozyme*® (discovered by *Genentech*) for the treatment of cystic fibrosis. Interleukin-12 and the TNF-receptor fusion protein Tenefuse from *Roche*'s own research groups in Nutley and Basel as well as several humanized monoclonal antibodies licensed in from, biotech companies are in clinical trials for the treatment of severe diseases such as sepsis, cancer, acute transplant rejection.

Using recombinant proteins as pharmacological tools and targets, several research groups at *Roche* have made good progresses in the discovery of novel drug candidates in the fields of immunology and inflammation. After the introduction of *Saquinavir*®, the first HIV protease inhibitor worldwide, as a new class of antiviral AIDS drugs, the *Roche* research is now focused on similar targets of other highly infectious viruses.

This overview of the past and present achievements in drug research at *Roche* is not complete without a reference to the broad and deep engagement of the scientists and research teams in the *Roche* laboratories as well as in the hospitals, working for the cure of patients with great commitment and confidence.

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