Pharma in Transition: new approaches to drug development at F. Hoffmann-La Roche & Co, 1960–1980

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Introduction

> [...] chemistry is at Roche's disposal just like a good wife, reliable, cooperative, maybe sometimes a little bit smiling with the knowledge that everything which had been realized came to a very great extent from her.[3]

The pharmaceutical industry transforms knowledge into drugs, and often into money. Today, drug innovation is based on knowledge produced by complex networks including pharmaceutical companies, biotechnology start-ups, and academic laboratories. It results from a combination of innovation strategies, for example research into the basic mechanisms of disease and drug action, using a series of molecular biology technologies such as

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3 Historisches Archiv Roche (HAR) FE.0.4 – 103593 h: 'Continuity in Chemistry Research', memorandum submitted by Otto Isler, head of chemical research at Roche, 5.6.1969, p. 1.

recombinant DNA or monoclonal antibodies. The laboratory scientists involved often assume multiple roles in academia and industry.

This oversimplified picture of what has been called the 'biotechnological revolution' reflects the perception that drug development has entered a new era with distinctive social, economic, cultural and scientific characteristics.[4] In this paper, we investigate the transition into the biotechnology era of a major pharmaceutical company, F. Hoffmann-La Roche & Co (Roche),[5] from the perspective of its top research management, and focus specifically on drug development strategies. We describe *how* new approaches to drug innovation, emphasizing biological[6] research instead of chemical synthesis, were introduced in the 1960s. Our paper also tries to explain *why* Roche managers and scientists introduced these changes. We argue that at least four different factors motivated this transition: diminishing returns from previous modes of drug innovation, tighter FDA drug approval policies, isolation from academic biological research networks, and expansion of the management's time horizon towards long-term planning. This paper thus constitutes a contribution to the history of both the pharmaceutical industry and the management of scientific research in the twentieth century.

The standard picture of the 'biotechnology revolution' stands in sharp contrast with the description of two earlier drug innovation regimes: the

4 On biotechnology, see M.D. McKelvey, *Evolutionary Innovations: the business of biotechnology* (Oxford: Oxford University Press, 2000); M. Kenney, *Biotechnology: the university-industry complex* (New Haven: Yale University Press, 198); S. Krimsky, *Biotechnics & Society: the rise of industrial genetics* (New York: Praeger, 1991); L. Orsenigo, *The Emergence of Biotechnology: institutions and markets in industrial innovation* (London: Pinter Publishers, 1989); R. Loeppky, *Encoding Capital: the political economy of the Human Genome Project* (New York and London: Routlege, 2005).

5 The company changed its name from 'F. Hoffmann-La Roche & Co.' to 'Roche Holding AG' in 1989.

6 The Roche management and scientists used the terms 'biological' and 'biochemical' to designate a variety of laboratory approaches, ranging from metabolic studies to fundamental research in virus genetics.

extractive and the synthetic.[7] These regimes are best characterized as a given combination of research strategies and institutional structures. The first came into being in the late-nineteenth century and relied on a strategy based on the chemical extraction of natural substances from plants and animals. It was mainly associated with the creation of small pharmaceutical firms. The second regime arose in the early-twentieth century, supplementing, but not replacing, the previous one. Its main strategy consisted in synthesizing structural variations of chemicals with known pharmacological effects and selecting the most promising variants through a screening procedure, i.e. testing the chemical compounds for pharmaceutical activity in animals, tissues or cells. It was generally associated with the establishment of in-house research laboratories, institutionalized relationships with academia, and the rise of multinational firms.

There exists no strong consensus regarding the origins, extent and precise characteristics of the historical transition towards the present mode of drug innovation. Defining a new innovation regime would therefore be premature. The most common explanation for this transition, however, is that it has been triggered by the invention of recombinant DNA technologies in the early 1970s, by changes in the market economy, in particular the availability of venture capital, and by amendments to intellectual property legislations in the United States. All of these developments were indeed important for the creation of start-up biotech companies, one of the key new players in this transition.[8] In the 1980s, the large drug companies began

7 V. Walsh, 'Paradigms in the evolution of life sciences research, and the changing structure of the innovation organization', in K. Grandin et al. (eds), *The Science-Industry Nexus: history, policy, implications* (Sagamore Beach: Science History Publications, 2004), pp. 189–221. We do not follow the author in her use of the term 'paradigm' because we do not feel that it conveys the institutional dimension we would like to stress, in combination with the cognitive dimension congruent with the Kuhnian origins of the term. In addition, the co-existence of paradigms stressed by the author differs from Kuhn's notion of paradigm replacement through scientific revolutions.

8 R. Teitelman, *Gene Dreams: Wall Street, academia, and the rise of biotechnology* (New York: Basic Books, 1989); S. Wright, 'Recombinant DNA technology and its social transformation, 1975–1982', *Osiris*, 2nd Series, 2 (1986): 303–360; G. Dutfield, *Intellectual Property Rights and the Life Science Industries: a twentieth century history* (Aldershot:

to adopt the new technologies for drug development, either by cooperating and eventually acquiring start-up companies, by incorporating new in-house capabilities, or by establishing collaborations with academic researchers.[9] Adopting a much broader perspective, the historian of science Robert Bud has stressed the century-long continuity of biotechnology as a vision and as a way of exploiting biological processes for production purposes.[10] Taking a middle ground, economic historians have underlined that only in the 1960s and 1970s did the amount of available fundamental biological knowledge make investments in biological research profitable for pharmaceutical firms, leading to changes in drug development strategies.[11]

Today one of the world's largest drug companies, Roche has lived through the different transitions outlined above. Like many of its major competitors in the pharmaceutical sector, Roche was founded in the late-nineteenth century as a chemical firm. According to business historian Alfred D. Chandler Jr., Roche is currently a leader in genetic engineering and has played 'a significant role in building the infrastructure of the emerging biotechnology revolution'.[12] Thus it represents a good case study through which to explore the transformation of the pharmaceutical industry. Even in the early 1960s, i.e. before recombinant DNA, a profound change became apparent at Roche. The Roche management began considering new drug development strategies and introduced new approaches based on

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Ashgate, 2003); D.J. Kevles, 'Diamond v. Chakrabarty and Beyond: the political economy of patenting life', in A. Thackray (ed.), *Private Science: biotechnology and the rise of the molecular sciences* (Philadelphia: University of Pennsylvania Press, 1998), pp. 65–79.

9 L. Galambos and J.L. Sturchio, 'Pharmaceutical Firms and the Transition to Biotechnology: a study in strategic innovation', *Business History Review*, 72 (1998): 250–278.

10 10 R. Bud, 'Biotechnology in the twentieth century.' *Social Studies of Science*, 21 (1991), pp. 415–457.

11 A. Gambardella, *Science and Innovation: the US pharmaceutical industry during the 1980s* (Cambridge: Cambridge University Press, 1995), pp. 22–26. For a similar quantitative argument see Walsh, 'Paradigms in the evolution of life sciences research', p. 193; also A.D. Chandler, *Shaping the Industrial Century: the remarkable story of the evolution of the modern chemical and pharmaceutical industries* (Cambridge and London: Harvard University Press, 2005).

12 Chandler, *Shaping the Industrial Century*, pp. 9–10, 15, quotations: pp. 241, 243.

fundamental biological research. The main objective was no longer solely to understand the chemical and pharmacological properties of drugs, as in the synthetic regime, but also to explain the molecular mechanisms of drug action and the precise biological targets of drugs. In other words, Roche was undertaking a transition from a strategy of drug development centred on chemistry to another centred on biology. 'Rational drug design' became the motto for this new approach.[13]

Noting that this transition was already underway in the 1960s at Roche does not explain why it took place. Sciences can provide new opportunities for a company only if they are interpreted as opportunities by the company management and its scientific staff. Every company management has to 'read' its own scientific, economic, social and organizational situation and environment in order to decide what changes are to be made.[14] By focusing on the discussions among the Roche management in charge of research planning and on the actual research projects that were carried out in the laboratories, we can thus illuminate how and why fundamental biological research came to be viewed as promising or even necessary for drug innovation.

The transition towards biological research represented a particularly sharp turn for Roche. Indeed, the company had not previously engaged in work on vaccines and had only maintained a very limited research program on antibiotics. Furthermore, it did not rely heavily on biological modes of drug production. Thus, Roche hardly possessed any in-house experience and expertise with biological research, and its laboratory infrastructure was essentially that of a chemistry laboratory. In addition to this lack of internal resources, it possessed no contacts in the biological sciences to

13 Nevertheless, the previous chemical strategies of drug innovation were far from irrational. Even in the nineteenth century, when the first synthetic drugs were developed, analogy with extracted drugs or synthetic dyestuffs gave some guidance. Synthesizing chemical variants of a molecule of known properties and testing their effects was indeed a rational approach. See M. Weatherall, *In Search of a Cure: a history of pharmaceutical discovery* (Oxford: Oxford University Press, 1990), pp. 36, 150.

14 K. Lipartito, 'Culture and the practice of business history', *Business and Economic History*, 24 (1995): 1–41 (5–6).

match its century-long networks of personal and institutional collaborations with academic chemists.

The situation at Roche regarding biological research and collaboration was quite typical for a chemistry-based pharmaceutical company. The few biologists or medical researchers who worked in these companies were mainly involved in screening compounds synthesized by organic chemists for pharmacological activity or in testing drugs for toxicity. Other pharmaceutical companies, such as Eli Lilly or Merck, had established more extensive collaborations with academic biomedical laboratories, or even hired biomedical researchers as early as the inter-war period.[15] Most of them, however, were involved in developing improved biological production methods, not in investigating fundamental biological questions.

In some cases, such as the endocrine drugs, vaccines or antibiotics, the contribution of biological research was of a more fundamental nature. However, after the Second World War, with the establishment of the State as the main patron for scientific research and with increased funding for the academic biological sciences, biological researchers became less willing to work for industry and doing so lost much of its prestige.[16] Thus, even though the case of Roche might be particularly revealing with regard to chemistry-based companies, the transition we analyse represented a serious challenge to the pharmaceutical sector as a whole in the post-war period.

Our historical reconstruction of the transition undergone by Roche in the 1960s relies, among other sources, on the minutes of the Roche Research

15 J.P. Swann, *Academic Scientists and the Pharmaceutical Industry: cooperative research in twentieth-century America* (Baltimore: John Hopkins University Press, 1988); N. Rasmussen, 'The Forgotten Promise of Thiamin: Merck, Caltech biologists, and plant hormones in a 1930s biotechnology project', *Journal of the History of Biology*, 32 (1999): 245–261; idem, 'The Moral Economy of the Drug Company-Medical Scientist Collaboration in Interwar America', *Social Studies of Science*, 34 (2004): 161–185; J.-P. Gaudillière, 'Better Prepared than Synthesized: Adolf Butenandt, Schering Ag and the transformation of sex steroids into drugs (1930–1946)', *Studies in History and Philosophy of Biological and Biomedical Sciences*, 36 (2005): 612–644.

16 N. Rasmussen, 'Of "Small Men", Big Science and Bigger Business: the Second World War and biomedical research in the United States', *Minerva*, 40 (2002): 115–146; Swann, *Academic Scientists and the Pharmaceutical Industry*, epilogue.

Management Group (RRMG) and the scientific reports submitted by the company's researchers to this managerial board. The RRMG was founded in 1956 and composed of a small nucleus of managers of the company's three main research sites in Switzerland, the United States, and Great Britain. The group's original duty was to discuss commercial, chemical, and clinical aspects of research in order to coordinate research activities at Roche.[17] Its members belonged either to the general direction responsible for the whole firm including both the parent house in Basel and the subsidiaries, or they were part of one of the local executives in the USA or the UK. The RRMG's first chairman was the chemist Placidius A. Plattner, who had been managing director in charge of research since 1952.[18] Occasionally the RRMG meetings were also attended by Roche employees responsible for a particular area of research or by outside experts.[19]

The discussions taking place within the RRMG were exempt from the necessities of daily business as well as the constraints of public relations. The group's meetings were 'undisturbed by telephone calls and intrusions of outsiders', and its members would have 'the leisure and time to really let [their] hair down and work out the problems facing [them] continually'.[20] In addition, a number of scientific reports were submitted to the RRMG, in which researchers at Roche could express their opinions vis-à-vis management more extensively.[21] Understandably, the minutes of the RRMG and

17 HAR FE.0.4 – 101129 a: Program of the first RRMG meeting, 25.–30.6.1956.

18 H.C. Peyer, *Roche. Geschichte eines Unternehmens 1896–1996* (Basel: Editiones Roche, 1996), p. 173. Other early members of the RRMG were the chemist Max Furter, member of the general direction since 1952 and in charge of manufacturing of specialities; the medical doctor and chemist Alfred Pletscher, head of medical research at Roche Basel since 1957 and Plattner's successor since 1967; the chemist Otto Isler, head of chemical research at Roche Basel; Lawrence D. Barney, president of Roche USA; the medical doctor Elmer L. Severinghaus and the chemist John Aeschliman, both executives at Roche USA; and the chemist Alexander Morrison, head of research at Roche UK.

19 HAR FE.0.4 – 101129 a: Placidius A. Plattner to Roche President Albert Caflisch, 29.11.1957.

20 HAR FE.0.4 – 101129 a: Minutes of the RRMG meeting, 24.–30.4.1957, add. to p. 1.

21 HAR FE.0.4 – 101129 a: Placidius A. Plattner to Roche President Albert Caflisch, 29.11.1957.

the reports submitted to this managerial board shed a different light on Roche's transition into the biotechnology era than do its published annual and business reports. They give unique insight into the vision and rationale of the management in charge of scientific research in a major pharmaceutical company during the second half of the twentieth century.[22]

Extraction and Synthesis at Roche

Before we turn to the transition undergone by Roche in the 1960s and 1970s, it is important to understand the research strategies and institutional arrangements on which the company relied in the first half of the twentieth century. In contrast to its local Swiss and German competitors, such as Ciba, Sandoz and Bayer, Roche did not evolve out of the chemical dyestuff industry.[23] Drug development at Roche was rooted in the chemical extraction of pharmacologically active natural products, a procedure that

22 However, neither the minutes nor the reports are delivered completely in the Roche Archives. We therefore intend to outline the broader lines of discussion rather than to reconstruct the exact processes of decision making at Roche.

23 The German dyestuff manufacturer Bayer created its pharmaceutical division in 1888, Ciba manufactured its first drugs around 1900 and created a 'Biologische Abteilung' in 1908. Sandoz produced analgesics beginning in 1895 and created its 'Pharmazeutische Abteilung' in 1917. G. Meyer-Thurow, 'The Industrialization of Invention: a case study from the German chemical industry', *Isis*, 73 (1982): 363–381; T. Straumann, *Die Schöpfung im Reagenzglas. Eine Geschichte der Basler Chemie* (Basel und Frankfurt a. M.: Helbing & Lichtenhahn, 1995); P.C. Waldmeier, 'Pharma-Forschung bei Ciba-Geigy und ihren Vorgängerfirmen CIBA und Geigy', in Athineos Philippu (ed.), *Geschichte und Wirken der pharmakologischen, klinisch-pharmakologischen und toxokologischen Institute im deutschsprachigen Raum* (Innsbruck: Berenkamp, 2004), pp. 858–863; H. Fritz, *Industrielle Arzneimittelherstellung. Die pharmazeutische Industrie in Basel am Beispiel der Sandoz AG* (Heidelberger Schriften zur Pharmazie- und Naturwissenschaftsgeschichte, 10) (Stuttgart: Wissenschaftliche Verlagsgesellschaft, 1992). See also A.S. Travis, *The Rainbow Makers: the origins of the synthetic dyestuff industry in Western Europe* (Bethlehem: Lheigh University Press, 1993).

had been established in the early-nineteenth century.[24] From the inter-war period onwards, however, the company shifted towards chemical synthesis, and by the 1960s it had become one of the world's largest manufacturers of synthetic drugs and vitamins. Drug development at Roche was now dominated by chemical synthesis; chemists occupied the leading positions in its management, and the company maintained close relationships with the chemical laboratories of Swiss universities. Alfred Pletscher, former head of research, summarized the company's development in the first half of the twentieth century by concluding that the 'traditional strength of Roche lies in synthetic chemistry'.[25]

Roche was founded in Basel in 1894 by the merchant Fritz Hoffmann and the apothecary Max Carl Traub as a spin-off of a small business that produced pharmaceuticals and commodity chemicals.[26] The growth of the company until the First World War relied mainly on sales of plant and animal extracts. The chemists Emil C. Barell and the apothecary Carl F. Schaegers, who both joined the company in 1896, initiated a research program on plant and organ extracts based on techniques they had learned when working at the university. Barell, who eventually became general director of Roche, had studied chemistry at the Swiss Federal Institute of Technology (ETH) in Zurich and the University of Bern. Schaegers had studied pharmacology in Munich and later at the University of Bern had worked together with the physician Theodor Kocher, who received the Nobel Prize in 1909, to investigate the extraction of the active substance of the thyroid gland. Since the late 1890s, Roche had sold a number of plant extracts, and from 1911 onward, the company launched a series of gland extracts, some of which were sold until after the Second World War.

The development of new drugs at Roche had often been guided by the experiences of pharmacologists and physicians working in academia, whom Roche's management and researchers had known personally. The company researchers themselves were in charge of improving the efficiency

24 Weatherall, *In Search of a Cure*, p. 20.

25 Pletscher, '25 Jahre Roche-Forschung', p. 25.

26 If not indicated separately, the following remarks on the history of Roche are based on Peyer, *Roche*.

of the chemical extraction processes in order to lower production costs and achieve high levels of purity.[27] Before the First World War, Roche set up an analytical laboratory to test the extracted products (Fig. 1). The pharmacological effect of most of the drugs launched by the company had already been known beforehand, and pharmacological research concentrated only on the toxicity and the effectiveness of the extracts. The cough syrup Sirolin for instance – one of Roche's first successful products, launched in 1898, and marketed until the 1950s – was composed of a chemically modified plant extract from a American tropical tree, a substance that had been assumed to be of therapeutic value as early as the mid-nineteenth century (Fig. 1).

During the inter-war period, Roche started manufacturing synthetic sedatives, vitamins and fine chemicals, and it strove to replace its extracted natural products with synthetic analogues. In particular fields such as pain killers, new synthetic compounds were considered less harmful than the conventional opium extracts, and the 1912 International Opium Convention restricting the use of opium forced the company to continue the search for alternatives.[28] In the early 1920s, the company launched its first semi-synthetic drug, the sedative Allonal.[29] Vitamins also became one of Roche's most important synthetic products. In the early-twentieth century, the concept of diseases due to deficiency of food factors present in

27 Until 1907, Swiss patent law did not protect chemical processes, which allowed companies to imitate their foreign competitors, especially German companies. However, the 1907 legislation was also prompted by the fact that the Swiss chemical industry no longer relied on imitation, as it had done throughout the nineteenth century. An appraisal of the extent to which Roche imitated production processes during its early years of existence would require further research. N. Stettler, 'Erfindungen', in *Historisches Lexikon der Schweiz*, [electronic publication, www.dhs.ch], 6.12.2004; Straumann, *Die Schöpfung im Reagenzglas*, pp. 132–134; J. Tanner, 'The Swiss pharmaceutical industry: the impact of industrial property rights and trust in the laboratory, 1907–1939', in A.S. Travis et al (eds), *Determinants in the Evolution of the European Chemical Industry, 1900–1939* (Dodrecht: Kluwer, 1998), pp. 257–272.

28 Peyer, *Roche*, pp. 94, 99.

29 Allonal was composed of an analgesic compound called amidopyrine, which had already been synthesized in the nineteenth century, and allylisopropylbarbituric acid synthesized by the Roche chemist Ernst Preiswerk. Weatherall, *In Search of a Cure*, pp. 36–37; Peyer, *Roche*, p. 94.

Figure 14.1 The Roche speciality Sirolin, 1910. © Historisches Archiv Roche.

trace amounts in normal diet had become widely accepted. Organic chemists succeeded in isolating the first vitamins, and nutritional scientists were enthusiastic about the newly discovered group of organic compounds. By the late 1920s, vitamins had become very fashionable and the subject of health propaganda in newspaper articles, radio broadcasts, and popular guides.[30] In 1933, Roche bought the patent rights for a synthetic pathway to vitamin C, and in the following decades, Roche purchased the rights to other synthetic vitamin pathways from university researchers, while contributing to the development of its own new synthetic processes.[31] Otto Isler for example, who joined Roche in 1936 after receiving his doctorate in chemistry at the ETH in Zurich and later became head of chemical research at Roche, contributed to the company's success in the vitamin business by discovering various vitamin synthesis pathways.[32] Eventually, Roche became one of the world's largest manufacturers of synthetic vitamins.

The development of chemical synthesis went hand-in-hand with an expansion of the company's in-house research capabilities. In contrast to their local and German competitors who started their business activity as dyestuff manufacturers in the nineteenth century, Roche did not dispose of extended facilities for research in synthetic chemistry. Therefore, new laboratory buildings were built as well as facilities for biological screening. Between 1924 and 1944, the number of researchers employed by Roche rose from 26 to 75.[33] As early as 1905, Roche had opened a branch office in

30 Weatherall, *In Search of a Cure*, chapter 7; S.M. Horrocks, 'The Business of Vitamins: nutrition science and the food industry in inter-war Britain', in H. Kamminga and A.Cunningham (eds), *The Science and Culture of Nutrition, 1840–1940* (Amsterdam and Atlanta: Rodopi, 1995), pp. 235–258 (238–239); R.D. Apple, '"They Need it Now". Science, advertising and vitamins 1925–1940', *Journal of Popular Culture,* 22 (1988): 65–83.

31 For more on this, see Beat Bächi's contribution to this volume.

32 M. Bürgi, *Die Anfänge der industriellen Vitaminproduktion. Fotografien aus dem Historischen Archiv Roche* (Basel: Historisches Archiv Roche, 2004); K. Bernhard, 'Otto Isler', in *Historisches Lexikon der Schweiz,* [electronic publication, www.dhs.ch], 29.7.2005.

33 By the end of the war, researchers counted for a little more than two percent of the total personnel. Peyer, *Roche*, p. 139 and pp. 159–160.

New York, where a research department had been created five years later.[34] In 1929, the US branch office moved to Nutley, New Jersey. Its research department continuously expanded and, by the end of the Second World War, it employed more chemists than the site in Basel. A third but significantly smaller research infrastructure was established in Welwyn Garden City, England, in 1938. In the same period, the company had also settled in many other European countries and eventually in China, Japan and South America. In most of these places, Roche maintained production facilities with limited research capabilities in order to support production engineering.

After the creation of larger in-house research facilities, the chemists working at Roche began publishing in international scientific journals.[35] The focus on chemical synthesis and the increased scientific status of Roche researchers made it possible to develop new collaborations with some of the most renowned academic chemists working in Swiss universities (especially the ETH and the University of Zurich) such as Paul Karrer (Nobel Prize 1937), Leopold Ruzicka (Nobel Prize 1939), and Tadeusz Reichstein (Nobel Prize 1950). As far as clinical research was concerned, like other pharmaceutical companies, Roche relied on the work of private physicians who used and evaluated the company's products in their medical practices.[36] In some cases, toxicological problems did not appear until a drug had been widely used for medical treatment, and several compounds had to be withdrawn from the market.[37]

34 For the development of Roche USA see 'Roche in Amerika, 1905–1965', *Roche Zeitung*, 1 (1966): 2–19.

35 The Science Citation Index lists 16 articles published by the chemists Franz Elger, Markus Guggenheim and Ernst Preisewerk until 1944, and another 16 articles published by members of the laboratories at Roche Nutley; cf. also E. Gwinner and B. Dalle Carbonare, 'Roche Pharma Research from the Past to the Present', *Chimia*, 50 (1996): 514–518 (516).

36 Peyer, *Roche*, provides only very little insight into the history of clinical research at Roche; cf. also Swann, *Academic Scientists and the Pharmaceutical Industry*.

37 This was the case for the Allonal ingredient amidopyrine. Weatherall, *In Search of a Cure*, p. 37.

The impact of the Second World War on research at Roche was manifold. As early as December 1938, Roche's administrative board had decided to concentrate increasingly on the US and Great Britain. The board limited the scheduled expansion of the Basel research site in favour of the research sites in Nutley and Welwyn. The decision was partly due to the upcoming war in Europe. Furthermore, in May 1940, when Germany invaded France, Roche's general director Emil C. Barell left Switzerland and moved to Nutley. Several senior scientists from the headquarters in Basel accompanied him, and contributed to the development of Nutley's research department until 1945. During the war, Roche Nutley became the most important research site of the company. This corresponded to a business strategy of 'decentralized growth'. Roche management tried to minimize risk by maintaining its business activities both in European countries, including Germany, and in the United States. But by 1941, revenues at Roche Nutley had grown rapidly. By the end of the war, the US subsidiary accounted for over 50 percent of the company's total revenues, which rose from approximately 65 million Swiss francs in 1939 to 177 million in 1945.[38] After the war, the company needed to improve the coordination of its increasingly decentralized research facilities, located in Switzerland, the United States and United Kingdom. The Roche Research Management Group was founded in 1956 to address this challenge. Wartime also strengthened the company's emphasis on synthetic vitamins. In its 1945 annual report, the administrative board of Roche stated that the 'effects of the war gave rise to an increasing demand for our products, especially for those suited to alleviate the pain that resulted from destitution and malnutrition'.[39] In other words, wartime food shortages and military needs had increased the demand for vitamins during these years. Among the ten top-selling products of Roche, vitamin-specialities registered the strongest growth

38 L. Straumann and D. Wildmann. *Schweizer Chemieunternehmen im 'Dritten Reich'* (Veröffentlichungen der Unabhängingen Expertenkommission Schweiz – Zweiter Weltkrieg, Vol. 7) (Zürich: Chronos, 2001), pp. 177–186.

39 'Bericht des Verwaltungsrates der Firma Hoffmann-La Roche', 1945, without paging; cf. also Peyer, *Roche*, p. 175.

in sales between 1941 and 1945, with the sole exception of the synthetic compound Prostagmin, a drug used to treat muscular diseases.[40]

Between 1947 and 1963, the total revenues of Roche's pharmaceutical products grew from 154 to 930 million Swiss francs without any major acquisition.[41] Vitamins and sulphonamides, a synthetic antibacterial agent, were Roche's best-selling products throughout the 1950s, and in the early 1960s the company launched another series of best-selling drugs, the synthetic benzodiazepine tranquillizers Librium and Valium. Sulphonamides were a class of synthetic dyestuff derivatives that had already been developed for medical use in the 1930s by researchers at the Bayer laboratories and the Pasteur Institute in Paris.[42] At the end of the 1940s, Roche launched its own sulphonamide, the lucrative Gantrisin.

Both the sulphonamide Gantrisin and the benzodiazepines Valium and Librium had been developed at Roche Nutley. The development of the latter illustrates the fact that, under the synthetic regime of drug development, new drugs were being developed without extensive knowledge about their biological mode of action. In 1955, the chemist Leo Sternbach, who had been an assistant of Leopold Ruzicka at the ETH in Zurich and who had joined Roche in 1940, succeeded in synthesizing the first synthetic benzodiazepine (chlordiazepoxide). The new compound showed a tranquillizing effect in animals. The company initiated clinical trials and finally brought Librium to market in 1960.[43] At the time when Sternbach and his colleagues developed Librium, Roche did 'not do a great deal of internal fundamental work on the biochemistry of mental disease'. Only a small group was kept active in this field 'in order to maintain contact with general progress'.[44] The reasons why the newly developed compound had a tranquillizing and anxiolytic effect were completely unknown, and of only marginal importance to the development of the drug. Indeed, the mode

40 Straumann and Wildmann, *Schweizer Chemieunternehmen im 'Dritten Reich'*, p. 270.
41 Information of Alexander Bieri, head of the Historisches Archiv Roche, 16.5.2006.
42 Weatherall, *In Search of a Cure*, pp. 150–153.
43 A. Bänninger et al., *Good Chemistry: the life and legacy of valium inventor Leo Sternbach* (New York etc: McGraw-Hill, 2004), pp. 49–52.
44 HAR FE.0.4 – 101129 a: Minutes of the RRMG meeting, 15.–23.10.1956, p. 4.

of action of benzodiazepine molecules on neurotransmitter receptors was only elucidated in the 1980s.[45]

Because benzodiazepines were a new class of pharmaceutical substances, Roche was able to assure large patent protection and develop a series of benzodiazepine compounds. By 1963, the new drugs had already realized the highest revenues of all Roche products; vitamins and sulphonamides came second.[46] From a medical point of view, the benzodiazepine tranquillizers were superior to their prede cessors, e.g. the barbiturates, because they did not show any adverse side-effects and overdose was not lethal. Enthusiastically, the popular press in the United States called the tranquillizers 'Happiness Pills' or 'Emotional Aspirin'.[47] Valium became the world's best-selling 'middle-class drug', and the single most prescribed drug in the United States.[48] By the end of the 1960s, Roche achieved over 50 percent of its total revenues with psychotropic drugs.[49]

During the same period, the company significantly enlarged its research capacities worldwide. In 1962, the total number of employees at the Roche research department in Basel reached 700.[50] Meanwhile, research at Roche Nutley had grown to a comparable extent, and eventually surpassed Basel in terms of expenditure.[51] Total research expenditure quadrupled between 1952 and 1962. Between 1958 and 1967, the contribution of Roche Basel's organic chemists consisted of approximately two thousand new compounds per year that were chemically synthesized or isolated and submitted to biological screening.[52]

45 Pletscher, '25 Jahre Roche-Forschung', p. 20–24.

46 HAR FE.0.4 – 101129 a: Minutes of the RRMG meeting, 13.–18.6.1963, p. 60.

47 S.L. Speaker, 'From "Happiness Pills" to "National Nightmare": changing cultural assessment of minor tranquillizers in America, 1955–1980', *Journal of the History of Medicine and Allied Sciences*, 52 (1997): 338–376 (347); M.C. Smith, *Small Comfort: a history of the minor tranquillizers* (New York etc.: Praeger, 1985).

48 D. Herzberg, "The Pill You Love Can Turn on You": feminism, tranquillizers, and the valium panic of the 1970s', *American Quarterly*, 58 (2006): 79–103 (79, 80).

49 HAR FE.0.4 – 101129 c: 'RRMG 1969', undated presentation, p. 5.

50 Peyer, *Roche*, p. 187.

51 HAR FE.0.4 – 102852: Untitled memorandum of Kurt Feinstein, 17.6.1969.

52 HAR FE.0.4 – 103593 e: 'New Research Functions and Activities', report submitted by Prof. A. Studer and Dr Ch. Polzer, 14.5.1968, table 2.

The Shift towards Molecular Targets

By the mid-1960s, researchers and managers at Roche became increasingly dissatisfied with the traditional approach to drug development, i.e. chemical synthesis and biological screening. A number of scientific reports submitted to the Roche Research Management Group (RRMG) prompted discussions among its members on whether the company should reorient its research activities and spend more time and money on fundamental biological research instead of the traditional chemical approach. Fundamental biological research was expected to provide detailed knowledge of normal and pathological biological mechanisms and offer new opportunities for drug development. The stronghold of organic chemistry was beginning to be challenged within the company.

Biological research on the mode of action of particular drugs was not completely lacking at Roche in the previous decades, but it was maintained on a very limited scale. Until the end of the 1950s, the RRMG rarely discussed the need to reinforce biological approaches, such as antiviral research, and generally considered them as either too expensive or unpromising for the development of new drugs. Only in selected therapeutic fields, such as the biochemistry of mental diseases, did the RRMG decide to make limited efforts in fundamental biological research, but merely in order to monitor the progress of academic research, a common strategy among pharmaceutical companies.[53]

The Roche management also remained unwilling to engage in biological drug manufacturing. The RRMG refused to carry out research on biosynthetic antibiotics because Roche had 'more experience in chemical manufacturing than in fermentation'.[54] Some researchers therefore considered it too hazardous to enter the 'biosynthetic approach with all the

53 HAR FE.0.4 – 101129 a: Minutes of the RRMG meetings 15.–23.10.1956, p. 4, 16, 17, 19, and 24.–30.4.1957, p. 2, 20.–25.10.1957, p. 13.

54 HAR FE.0.4 – 101129 a: Minutes of the RRMG meeting, 15.–23.10.1956, p. 9.

risks and pitfalls involved in fermentation work'.[55] Similarly, in the field of viral diseases, the RRMG preferred the chemotherapeutic to the vaccine approach, even though the latter was considered to be 'most likely to produce immediate results'; a decision probably motivated by the fact that vaccines could not be manufactured synthetically, but also because research on vaccines would have overstrained the 'present personnel and facilities'.[56]

In the 1960s, the RRMG began to evaluate the prospects of 'rational' approaches to drug development, a term that first appeared in the RRMG minutes in 1967.[57] The topic had been raised by 1966 when scientists from the Roche laboratories in Welwyn submitted three reports on the 'future pattern of research' to the RRMG demanding considerable investments in biochemical and biological research.[58] All three reports stressed that the classical approach to drug development, combining chemical synthesis and biological screening, was increasingly dissatisfying. If for certain diseases the screening of potential drugs on animals was relevant to predict their action in the human body, the reports emphasized that no reliable screening tests existed for other diseases, such as psychiatric disorders. Furthermore, the sheer number of already existing drugs lowered the chances of finding new drugs by trial-and-error approaches alone. At this point, the chemist M. W. Parkes, researcher at Roche Welwyn and author of one of the reports, concluded that

> the drug industry must consider its position and revise its pattern of research. Since drugs are going to cost so much more to find, we must learn how to find them more reliably. [...]

55 HAR FE.0.4 – 103593 a: J. Herrero, M. Montavon, W. Mosimann, W. Rehm, G.E. Werner to the members of the RRMG, 17.5.1966.

56 HAR FE.0.4 – 101129 a: Minutes of the RRMG meetings, 25.–30.4.1960, p. 10, and 13.–18.6.1963, p. 2.

57 HAR FE.0.4 – 101129 b: Minutes of the RRMG meeting, 18.–23.5.1967, typescript entitled 'RRMG 1967', p. 69.

58 All three reports are entitled 'Future pattern of research', undated and submitted to the RRMG on the occasion of its 1966 meeting held between June 14 and 18. The authors are Alexander L. Morrison, head of research at Roche Welwyn, M.W. Parkes and R. F. Long. The reports are delivered in HAR FR.0.4 – 103593 a.

> Instead of starting with synthesis, stemming from a chemist's ideas, work should start from biochemical and biological investigation, based on the fundamental studies of others, and leading to a clarification of what the proposed drug is required to do and how it could do it, preferably in biochemical terms.[59]

Parkes underlined that the future development of research in the pharmaceutical industry would bring along the 'decline of the chemist from his present leading position'.[60] As a consequence, the report from Roche Welwyn claimed that the company should devote an increasing proportion of its research expenditures to biology and biochemistry.[61]

Two years later, the RRMG received a report evaluating drug development at Roche Basel during the past decade.[62] The report aimed at 'obtaining suggestions for the further procedure in the development of new drugs'. From 20.000 compounds tested during the period under investigation, 181 had been submitted to preliminary clinical trials and only seven had finally been introduced as specialities. None of the 181 molecules had been detected by 'submission of basically new compounds to a fixed, stereotyped battery of pharmacologic and chemotherapeutic tests', i.e. random screening. Instead, the compounds were the result of what has been called 'programmed screening', namely the molecular manipulation of chemical structures already known to have pharmacological action. But while random screening had obviously not been effective at all, molecular manipulation was not likely to generate entirely new drugs either. Furthermore, the report stated that successes like the discovery of the benzodiazepines could hardly be repeated and should be considered as resulting from an 'especially fortunate' combination 'of top scientists [...] and a large amount of luck'. The report therefore recommended to intensify 'basic research including

59 HAR FE.0.4 – 103593 a: 'Future pattern of research', undated report submitted to the 1966 RRMG meeting by M.W. Parkes, p. 4.

60 HAR FE.0.4 – 103593 a: 'Future pattern of research', undated report submitted to the 1966 RRMG meeting by M.W. Parkes, p. 1.

61 HAR FE.0.4 – 103593 a: 'The Future pattern of research', undated report submitted to the 1966 RRMG meeting by R. F. Long, p. 3.

62 HAR FE.0.4 – 103593 e: 'New Research Functions and Activities', report submitted by Prof. A. Studer and Dr Ch. Polzer, 14.5.1968.

biochemistry, immunology and experimental pathology' rather than 'a further increase in random screening', at least in fields where screening results had been disappointing. Other reports submitted to the RRMG argued in a similar way, highlighting the limits of the traditional approach to drug development and advocating new strategies to develop drugs more efficiently.[63]

Roche was by far not the only company facing difficulties in bringing new drugs to market. In the 1960s, the wave of new pharmaceutical products levelled off in general.[64] Roche badly needed new marketable compounds because the company had a very unbalanced product range and its sales were largely due to a single category of drugs: tranquillizers. For a member of the RRMG in charge of the commercial aspects of research at Roche, this situation entailed 'the well-known risk that too many eggs lie in the same basket, and that all the eggs could drop out once the basket gets a hole'.[65] The Roche management also had to worry about rising public concerns regarding psychotropic drugs. In the United States in particular, tranquillizer addiction and abuse had become a publicly debated issue throughout the 1960s.[66] The RRMG decided that the problem had to be addressed in the near future.[67]

In spite of the various arguments in favour of fundamental biological research, not all members of the RRMG were convinced. The chemist Otto Isler for instance insisted that:

> [...] chemistry is at Roche's disposal just like a good wife, reliable, cooperative, maybe sometimes a little bit smiling with the knowledge that everything which had been realized came to a very great extent from her. As you all know, Roche-earnings are

63 See for instance HAR FE.0.4 – 103593 e: 'Trends in Drug Research', undated report submitted by Dr Hines to the 1968 RRMG meeting, p. 1.

64 Chandler, *Shaping the Industrial Century*, p. 34.

65 HAR FE.0.4 – 101129 c: 'RRMG 1969', undated presentation, p. 5; cf. also HAR FE.0.4 – 101129 b: Minutes of the RRMG meeting, 18.–23.5.1967, typescript entitled 'RRMG 1967', pp. 28–29.

66 Speaker, 'From "Happiness Pills" to "National Nightmare"', pp. 348–353.

67 HAR FE.0.4 – 101129 b: Minutes of the RRMG meeting, 5.–8.6.1968, p. 5.

> due to sales of substances in the form of specialities or bulk and seldom or never in the form of theories or speculation.[68]

Isler considered the new biological approaches to drug development to be perhaps of theoretical, but hardly of practical interest. He therefore concluded that the future successes of Roche should rely on what he called 'conventional research', namely organic synthesis combined with biological screening. He admitted, however, that chemists should cooperate more closely with those in charge of biological and medical research. The chemist Alexander Morrison, head of research at Roche Welwyn and member of the RRMG, expressed similar provisos regarding new approaches to drug development, but for different reasons. He was convinced that in the future the economic prosperity of Roche would depend more on the drugs the company was already selling, than on the development of entirely new compounds. He therefore addressed the RRMG asking for a concentrated effort on the improvement of synthetic manufacturing processes in order to lower production costs and maintain the company's competitiveness.[69] However, Isler's metaphor of Roche and chemistry as husband and wife indicates that the position of chemistry at Roche had become clearly challenged – like the traditional marital model that had just come under fire in the counter-culture movements of the late 1960s.[70]

The field of antiviral research illustrates Roche's changing research priorities in the 1950s and 1960s. The development of an antiviral drug was pursued by Roche because its potential markets seemed even larger than those for antibacterial sulphonamides in which Roche was already heavily

68 HAR FE.0.4 – 103593 h: 'Continuity in Chemistry Research', memorandum submitted by Otto Isler, 5.6.1969, p. 1.

69 HAR FE.0.4 – 103593 b: 'Pattern of Future Research Activities in Welwyn', report submitted by Alexander Morrison, 9.5.1967, p. 3.

70 A. Marwick, *The Sixties: cultural revolution in Britain, France, Italy, and the United States, c.1958–c.1974* (Oxford: Oxford University Press, 1998), pp. 381–403; for Switzerland see E. Joris and H. Witzig (eds), *Frauengeschichte(n). Dokumente aus zwei Jahrhunderten zur Situation der Frauen in der Schweiz* (Zürich: Limmat Verlag, 1991), pp. 473–483.

involved.[71] In the 1950s, Roche had a modest antiviral research program that consisted in screening compounds randomly against a small number of viruses in tissue cultures and *in vivo*. However, between 1958 and 1967, the Basel research department only succeeded in preparing one antiviral compound for preliminary clinical trials, which finally did not show any satisfactory results.[72]

Because of this failure, the medical doctor and chemist Alfred Pletscher,[73] who had succeeded Placidius A. Plattner as managing director in charge of research and chairman of the RRMG, called for a 'new approach' to antiviral research.[74] Researchers at Roche repeatedly discussed the potential of the vaccine approach against viral diseases. But it would have entailed major investments or cooperation with a firm already well established in the vaccine business, since Roche did not have any experience in that field.[75] Virginius D. Mattia, a physician by training and president of Roche Nutley, outlined another antiviral approach, proposing that research should focus on viral nucleic acids.[76] As a result, Nutley formed a biochemical virology section within the department of chemotherapy, devoted to investigating the mechanisms of viral RNA replication in the host cell.[77] It was hoped that the results of this research would make it possible to develop a drug interfering with this mechanism. The rationale behind this research program on the molecular mechanism of viral infection was thus to identify appropriate molecular targets for an antiviral drug.

71 HAR FE.0.4 – 101129 a: Minutes of the RRMG meeting, 15.–23.10.1956, p. 16 and 25.–30.4.1960, p. 10.

72 HAR FE.0.4 – 103593 e: 'New Research Functions and Activities', report submitted by Prof. A. Studer and Dr Ch. Polzer, 14.5.1968, table 1.

73 Kunz, 'Alfred Pletscher'.

74 HAR FE.0.4 – 101129 b: 'RRMG Meeting 1967/(Notizen A. Pletscher)', 30.5.1967, p. 6.

75 HAR FE.0.4 – 103593 h: 'Antivirals', report submitted by Mr. Mosimann, 5.5.1969, p. 2; HAR FE.0.4 – 101129 a: Minutes of the RRMG meeting, 25.–30.4.1960, p. 10.

76 Peyer, *Roche*, p. 225.

77 HAR FE.0.4 – 103593 f: 'New Approaches to Antiviral Chemotherapy', report submitted by Roche Nutley, 21.5.1970.

In 1971, Roche Nutley organized an interdisciplinary meeting on antiviral and anticancer research. In his opening remarks, John J. Burns, biochemist and head of research at Roche Nutley, reaffirmed the need for a new approach to antiviral therapy, which Pletscher had mentioned a few years earlier but which had not yet been implemented systematically:

> It is evident, that random screening for antiviral and anticancer agents is a worthwhile approach and should not be abandoned. However, simultaneous basic research at the molecular level is indispensable if we are to comprehend the complexities of the biochemical and biological phenomena and use the acquired fundamental knowledge to design a rational program for antiviral and anticancer research.[78]

The participants at the meeting discussed viral RNA replication in the host cell, and other possible targets for antiviral drugs, such as virus penetration, virus assembly, or its release from the host cell. These targets began to be investigated by several research teams in Basel and Nutley in order to 'set up carefully controlled *in vitro* systems to measure the effect of chemical agents on any one or all of the steps involved in viral replication'.[79] A group of researchers in Basel, for example, started searching for an inhibitor of neuraminidase, i.e. an enzyme that plays a role in the virus release from the host cell. It was assumed that finding a compound that inhibits the enzyme could stop the virus proliferation in the infected organism.[80] It took, however, nearly another three decades until the first antiviral neuraminidase inhibitor was marketed. In 1999, GlaxoSmithKline and Roche both launched antiviral drugs that block the viral neuraminidase. Roche had not developed the compound in-house; instead it had purchased it from the biotechnology company Gilead Sciences Inc.[81] Even though Roche never developed its own neuraminidase inhibitor, this example illustrates

78 HAR FE.0.4 – 103593 i: 'Interdisciplinary Research Meeting. Antiviral Research, Anticancer Research', report submitted by Roche Nutley, 21.5.1971, introduction.

79 HAR FE.0.4 – 103593 i: 'Interdisciplinary Research Meeting. Antiviral Research, Anticancer Research', report submitted by Roche Nutley, 21.5.1971, p. 2.

80 HAR FE.0.4 – 103593 k: 'New Approaches to Antiviral Chemotherapy', report submitted by Mr. Mosimann, 5.5.1972, p. 2.

81 Cf. http://www.gilead.com

how, by the end of the 1960s, fundamental biological research had begun to play an increasingly important role for the company's new drug development strategies. This example also shows that while fundamental biological research was always viewed as an alternative to previous strategies, such as random screening, it was also seen as a way to reinforce them, for example by allowing the development of new test systems to assess the effects of drugs on specific molecular targets.

Raising Drug Safety Issues and the Need for Biology

In addition to the dissatisfaction with the effectiveness of conventional approaches to drug development, there was yet another reason why biological research became important at Roche during the 1960s. By 1963, the recently tightened drug approval policies in the United States provoked discussions among Roche managers and researchers on whether the company required more profound knowledge on the biological activity of drugs; knowledge that could neither be provided by synthetic chemistry, nor by animal testing alone.

In late 1962, the US Congress had passed the Kefauver-Harris Drug Amendments to ensure drug efficacy and greater drug safety. In the previous year, the German-based company Grünenthal had had to withdraw its thalidomide sleeping aid Contergan because of the strong suspicion that it was responsible for an alarming increase in malformations among newborn children in Europe. The FDA had not yet approved thalidomide, but the American company licensing the compound had already distributed the drug to over one thousand medical doctors for clinical investigations. Under the existing FDA laws and regulations, prescription drugs distributed for clinical investigations did not require FDA approval. The new Drug Amendments of 1962 considerably strengthened the control of clinical trials. From then on, FDA approval was necessary even for testing new compounds in clinical investigations. In early 1963, the FDA announced

new regulations that obliged a company to provide the agency with comprehensive information about compounds before testing them in clinical trials.[82] The Roche Research Management Group stated in June 1963 that these new requirements made it 'very difficult to bring new drugs to the first clinical trials' in the United States. Furthermore, the allegations against Contergan had been confirmed in 1962 and drug safety was becoming a matter of growing public concern. In view of this 'increased sensitivity to toxicological problems', the RRMG wanted the company to respond with a policy of 'frankness including informative action', 'defensive measures' and 'fundamental research'.[83]

What kind of fundamental research did the Roche managers have in mind? The 1962 FDA legislation had its most significant impact on clinical investigations. Under the new regulations, clinical trials with new drugs had to be scientifically planned by qualified investigators and reported in detail to the FDA.[84] But the new Drug Amendments also affected the pharmaceutical industries' pre-clinical testing practices.[85] Besides toxicological data, the FDA now also required information on drug metabolites (i.e. the small molecules resulting from the drug's breakdown in the organism) and

82 R.E. McFadyen, 'Thalidomide in America: a brush with tragedy', *Clio Medica*, 11 (1976): 79–93; G.P. Larrick, 'How the Food and Drug Administration evaluates New Drug Applications', *The Journal of new Drugs*, 4 (1964): 63–74.

83 HAR FE.0.4 – 101129 a: Minutes of the RRMG meeting, 13.–18.6.1963, p. 41. In October 1962, the Swiss regulatory board IKS also planned to tighten its regulations, but the minutes of the 1963 RRMG meeting do not mention this initiative explicitly. See also CIBA Firmenarchiv Vg 1.01 Verwaltung: Minutes of the 'Pharma Geschäftsausschuss', No. 39, 25.10.1962, paragraph 3.

84 A.A. Daemmrich, *Pharmacopolitics: drug regulation in the United States and Germany* (Chapel Hill and London: University of North Carolina Press, 2004); cf. also G.P. Larrick, 'New Federal Regulations for the Control of New Drug Testing in Humans', *The Journal of new Drugs*, 2 (1962): 373–384.

85 Daemmrich, *Pharmacopolitics*, p. 27. Laboratory research on a drug's toxicological effects had, of course, already been part of drug development before 1963, and had been required by the FDA for market approval since 1938. See H.M. Marks, *The Progress of Experiment: science and therapeutic reforms in the United States, 1900–1990* (Cambridge: Cambridge University Press, 1997), pp. 71–97.

on the drug's interaction with other chemicals.[86] The RRMG discussed these requirements taking into account a number of internal scientific reports on that issue. In 1966, a report submitted by Roche Welwyn to the RRMG underlined that it was becoming increasingly difficult to bring a new drug on the market, since many countries were requiring 'detailed information on the biological activity, both desirable and undesirable, of all new compounds before they can be tested clinically'.[87] Such information could not be provided on the basis of chemical synthesis and biological screening alone. The authors of the reports therefore requested that the company should 'intensify fundamental research' as well as increase the 'proportion of pharmaceutical effort devoted to biology'.[88] Two years later, another report concluded that to produce merely 'a new compound that had a desirable pharmacological action in man' was no longer sufficient anymore. Instead, more knowledge would be needed 'about the mechanism of action of the drug' and 'a reasonable understanding of its metabolism'[89] – knowledge that had been completely irrelevant for the development of earlier Roche products, such as the above-mentioned benzodiazepines.

The fact that research on drug metabolism had become more important after the thalidomide tragedy, is further illustrated by the way Roche's local competitor Ciba reacted to the withdrawal of Contergan. Four days after Grünenthal had to stop selling its sleeping aid, the management of the pharmaceutical division at Ciba discussed the consequences this had for the company. In particular, the managerial board decided to prepare the defence of the Ciba speciality Doriden. Like Contergan, this compound was used as a sleeping aid and was suspected of having similar effects on the human foetus. But the Ciba management was hoping that its own drug

86 Larrick, 'How the Food and Drug Administration Evaluates New Drug Applications', p. 69.

87 HAR FR.0.4 – 103593 a: 'Future pattern of research', undated report submitted by Alexander L. Morrison to the 1966 RRMG meeting, p. 1.

88 HAR FE.0.4 – 103593 a: 'Future pattern of research' undated report submitted by R. F. Long to the 1966 RRMG meeting, p. 3.

89 HAR FE.0.4 – 103593 e: 'Trends in Drug Research', undated report submitted by Dr Hines to the 1968 RRMG meeting, p. 2, cf. also HAR FE.0.4 – 101129 b: Minutes of the RRMG meeting, 5.–8.6.1968, p. 2 and 4.

could eventually step into the market gap opened by the Contergan affair. This hope was based on a study exploring the metabolism of Doriden, which was carried out by the biochemist Karl Bernhard, professor at the university of Basel, and two of his collaborators working at Ciba.[90] In their study, they concluded that because of the rapid and complete elimination of its metabolites, Doriden displayed no side- or after-effects and had a low toxicity. In view of these results, the authors were convinced that metabolic studies, i.e. studies on the biological mechanism of action of drugs, would be increasingly important for drug development:

> The general trend towards greater safety and reliability in human medical therapy has created the need for more information on the mode of action and fate of drugs in the organism. There is now reason to hope that by means of detailed metabolic studies it will often be possible to discover in good time those harmful side-effects of a preparation which do not appear until the patient has been under treatment for some considerable period and which in many instances are due to a cumulative action or to the building up of toxic metabolites.[91]

The most significant consequences of the new FDA regulation on pre-clinical research at Roche were, however, the indirect result of their economic impact. In view of the tightened FDA approval policies for clinical trials, the Roche research managers concluded that the company needed more reliable pre-clinical research strategies in order to avoid costly clinical investigations for compounds with an uncertain potential. In the above-mentioned reports submitted to the RRMG in 1966, Alexander Morrison, head of research at Roche Welwyn, stated that in many cases *in vitro* and *in vivo* tests could give a reliable guide to the efficacy of the drug in humans. But in other cases, such as rheumatic or psychiatric diseases, researchers would not know whether 'the pharmacological test procedures bear any

90 CIBA Firmenarchiv Vg 1.01 Verwaltung: Minutes of the 'Pharma Geschäftsausschuss', No. 12, 28.11.1961, paragraph 1.

91 H. Keberle, K. Hoffmann, K. Bernhard, 'Metabolism of Glutethimide (Doriden)', *Experientia*, 18 (1962): 105–111 (105, 110).

relationship to the clinical condition'.[92] The Welwyn researchers therefore requested that the company intensify fundamental biological research, hoping this would increase the chances that a new chemical compound would actually work in humans. The stakes had simply grown 'too high to gamble on the selection from compounds virtually randomly submitted to tests of doubtful relevance'.[93] The RRMG agreed and approved the plans of Roche Welwyn to enlarge its biological research facilities.[94]

Public concerns about drug safety and the strong reaction of the US regulatory authorities resulting in new economic constraints thus constituted another incentive for Roche to reorient its scientific tradition focused on organic synthesis, and to devote an increasing part of its resources to biological research.

The Roche Institute of Molecular Biology and New Relationships with Academia

The turn toward biological targeting also manifested itself in significant institutional changes at Roche. In 1967, the general management in Basel approved plans of Roche Nutley to build the Roche Institute of Molecular Biology (RIMB), an institution entirely devoted to fundamental biological research. In the following year, Roche built a similar institution in Switzerland, the Basel Institute for Immunology (BII).[95] Even though both institutions counted for only a relatively moderate part of the com-

92 HAR FR.0.4 – 103593 a: 'Future pattern of research', undated report submitted by Alexander L. Morrison to the 1966 RRMG meeting, p. 1 and 2.

93 HAR FE.0.4 – 103593 a: 'Future pattern of research', undated report submitted to the 1966 RRMG meeting by M.W. Parkes, p. 4.

94 HAR FE.0.4 – 101129 b: Untitled memorandum of Kurt Feinstein, 21.6.1966, p. 1 and 2; Thomas et al., 'Fifty years of Welwyn research'.

95 Pletscher, '25 Jahre Roche-Forschung', see p. 46.

pany's rising research expenditures,[96] they represented the introduction of a significantly different institutional culture. Indeed, these institutes offered academic working conditions where researchers were free to choose their research topics. This focus on fundamental, rather than applied, biological research, and the granting of academic working conditions, was perceived as a means to attract new scientific staff and develop close collaborations with biological researchers working in academia. (Fig. 3.)

Fig. 14.2 John J. Burns, Virginius D. Mattia and Sidney Udenfriend, groundbreaking ceremony for the RIMB, 1968. © Historisches Archiv Roche.

96 According to a cost projection submitted to the RRMG in 1971, total research expenditures in Europe and Japan were supposed to rise from 60 million Swiss francs in 1967 to more than 270 million in 1976, whereof only 5,5 percent were to be spent for the BII. Both institutions, the BII and the RIMB, employed approximately 200 persons by 1975. HAR FE.0.4 – 102852: 'Forschung: Fünfjahresvorschau', September 1971, and Peyer, *Roche*, p. 226.

The Roche Research Management Group had already discussed the establishment of 'an institution devoted to the study of one or more basic topics' in 1963.[97] Even though researchers at Roche had always been given a certain amount of opportunity to investigate problems of basic interest, no particular institutional setting had been created for this purpose so far.[98] Presumably, the discussions taking place at the RRMG meeting in 1963 had been influenced by the fact that, just a few weeks earlier, the local competitor Ciba had opened the 'Woodward Forschungsinstitut' in Basel. This institute consisted of a few laboratories housed in an industrial research building at Ciba. It was directed by Robert Woodward, a chemistry professor at Harvard University who was awarded the Nobel Price in 1965 for his work on the organic synthesis of natural products. Four to five times a year, Woodward came to Basel and held workshops with his collaborators at the Ciba institute. He also assumed the role of a scientific advisor for Ciba. Furthermore, the members of the institute were hired for a limited period only, much like postdoctoral fellows at American universities, and some of them eventually took over academic positions when they left Ciba.[99] But in contrast to the RIMB, the Woodward Institute clearly focused on chemical rather than biological research.

Four years after the first discussion had taken place within the RRMG, the project was finally realized after biochemists Sidney Udenfriend and Herbert Weissbach discussed plans to build a Roche institute for fundamental biological research in the United States with John J. Burns, head of research at Roche Nutley, in March and April 1967. They had known each other since the 1950s when working in the same laboratory at the NIH. In 1966 Burns had been appointed head of research at Roche Nutley in order to strengthen biological research within the company. The plans for the new institute were based on a rejected grant proposal for a Molecular

97 HAR FE.0.4 – 101129 a: Minutes of the RRMG meeting, 13.–18.6.1963, p. 41.

98 Cf. HAR FE.0.4 – 101129 b: Minutes of the RRMG meeting, 18.–23.5.1967, typescript entitled 'RRMG 1967', p. 31.

99 'Das Woodward Forschungsinstitut', special issue of *CIBA-Blätter*, 202 (March–April 1966); CIBA Firmenarchiv Vg 1.01: Minutes of the 'Direktionskomitee', No. 807, 4.6.1963, paragraph 7.

Pharmacology Institute at St. Louis University that Weissbach had submitted to the NIH in early 1967.[100]

Only a few weeks later, the company decided to build the RIMB, and the Roche management singed a charter stipulating that the institute would be 'wholly devoted to long range basic research designed to shed light on fundamental life processes'.[101] A number of early research projects at the RIMB were unrelated to any particular human diseases, such as those on the virus lambda, whose only victims are bacteria. Other projects aimed at understanding the basic mechanisms of protein synthesis and genetic regulation, or at determining the characteristics of biological macromolecules.[102] For example, members of the institute isolated and determined the amino acid sequences of neuropeptides, i.e. proteins, which play a role in the nervous system.[103] Other projects focused on interferon, i.e. a protein, which was expected to be useful in antiviral and anticancer therapy. This eventually led to the production of recombinant human interferon, Roche's first drug manufactured by genetically modified bacteria.[104] (Fig. 4.)

Other industrial companies had created institutions for fundamental research as early as the inter-war period, among them the chemical company Du Pont or the pharmaceutical companies Merck and Squibb. By establishing the new facilities, these firms had hoped to increase the chances of recruiting first-rate academic scientists and to improve their relations with

100 H. Weissbach, 'Reflections on the Roche Institute of Molecular Biology after 20 years', in J. Drews and F. Melchers (eds), *Research at Roche* (Basel: Editions Roche, 1989), pp. 231–259; S. Udenfriend, 'A Short History of the Roche Institute of Molecular Biology', *BioEssays*, 7 (1987): 278–280.

101 Weissbach, 'Reflections on the Roche Institute of Molecular Biology', p. 238.

102 Roche Institute of Molecular Biology, *Annual Report*, 1969.

103 S. Udenfriend, 'Neuropeptides, A Personal History', in Rao S. Rapaka and N. Dhawan Bhola (eds), *Opioid Peptides: an update* (NIDA Research Monograph Series 87) (Rockville: National Institute on Drug Abuse, 1987), pp. 1–9.

104 Weissbach, 'Reflections on the Roche Institute of Molecular Biology', pp. 253–254; see also Roche Institute of Molecular Biology, *Annual Report*. 1970, p. 5, HAR FE.0.4 – 103593 i: 'Interdisciplinary Research Meeting. Antiviral Research, Anticancer Research', report submitted by Roche Nutley, 21.5.1971, and HAR FE.0.4 – 101129 e: Minutes of the RRMG meeting, 16.–18.6.1977, p. 18.

academia.[105] Similar arguments were voiced within the Roche management in favour of building the RIMB. The Roche Research Management Group estimated that the 'higher the standard of research' at Roche, the easier the recruitment of first-class workers.[106] However, in Switzerland, it was difficult to find researchers or research institutions to collaborate with in the first place, since the modernization of biology in the universities was just beginning to take place,[107] while in the United States, molecular biologists didn't seem very inclined to work for industry. Indeed, Herbert Weissbach identified a 'stigma of working for industry' among his academic colleagues.[108] Furthermore, working conditions for biological researchers at American universities were fairly attractive due to generous federal funding.

Roche therefore tried to make its new research institution as attractive as possible to academic biologists by granting working conditions similar to those prevailing in academia, and the company management thereby accepted features which were entirely 'foreign to the Roche organization.'[109] According to the charter signed by the Roche management, the RIMB scientists enjoyed 'independence in their choice and pursuit of research

105 W.B. Carlson, 'Innovation and the Modern Corporation: from heroic invention to industrial science', in J. Krige and D. Pestre (eds), *Companion to Science in the Twentieth Century* (London and New York: Routledge, 2003), pp. 203–226 (218); Swann, *Academic Scientists and the Pharmaceutical Industry*, pp. 41–49; D.A. Hounshell, 'Continuity and Change in the Management of Industrial Research: the Du Pont Company, 1902–1980', in G. Dosi et al (eds), *Technology and Enterprise in a Historical Perspective* (Oxford: Clarendon Press, 1992), pp. 231–260.

106 HAR FE.0.4 – 101129 b: Minutes of the RRMG meeting, 18.–23.5.1967, typescript entitled 'RRMG 1967', p. 29.

107 HAR FE.0.4 – 101129 b: Minutes of the RRMG meeting, 18.–23.5.1967, typescript entitled 'RRMG 1967', p. 30, and 'Roche Forschung', an interview with Alfred Pletscher. *Roche Zeitung*, 1 (1968), pp. 43–48 (44); cf. also B.J. Strasser, *La Fabrique d'une nouvelle science: la biologie moléculaire à l'âge atomique (1945–1964)* (Florence: Olschki, 2006); M. Bürgi, 'Pharma, Politik und Polypeptide – Die Institutionalisierung der Molekularbiologie in Zürich, 1962–1971', *Traverse*, 3 (2005): 126–139; N. Stettler, *Natur erforschen. Perspektiven einer Kulturgeschichte der Biowissenschaft an Schweizer Universitäten 1945–1975* (Zürich: Chronos, 2002), pp. 181–192.

108 R.J. Bazell, 'Molecular Biology, "Corporate Citizenship and Potential Profit"'. *Science*, 174 (1971): 275–276 (275).

109 Weissbach, 'Reflections on the Roche Institute of Molecular Biology', pp. 242–243.

problems'. Their independence was also guaranteed architecturally. The institute was located in its own building, off the main industrial and research site, with a separate gate and roadway, and 24-hour access. Flexible work time, common in academic molecular biology laboratories, was also new to the Roche management. In addition, many of the Institute's members held formal appointments on nearby university faculties, such as Colombia University or New York University, and some served as executive editors of peer reviewed scientific journals such as *Molecular and Cellular Biology*. Even when advertising in the *New York Times* for the position of secretary to the new director, the RIMB stated it would 'give preference to applicants with work experience in an academic environment'.[110]

Figure. 14.3. Sidney Udenfriend, John J. Burns, Robert B. Clark and Renato Dulbecco bhind a model illustrating the molecular mechanism of protein synthesis in the cell, inauguration of the new RIMB building in 1971. © Historisches Archiv Roche.

110 Classified advertisement, New York Times (16 June 1968), p. W17.

The RIMB also offered a postgraduate education program and held international symposia on various topics of molecular biology. The second symposium organized in 1973, for example, was devoted to 'Genetic Recombination'.[111]

The strategy of creating an academic culture within the company seemed to have the desired effect. In 1969, Nutley reported to the RRMG:

> Excellent relations to academic institutions have been established. The academic world has received the whole project in such a good manner that an unexpected large number of distinguished scientists have applied for a job.[112]

In 1971, 128 scientists worked at the RIMB, and this number climbed up to 200 by 1975, many of them as postdoctoral fellows. According to the RRMG, it was the only industrial institution taking part in the 'Exchange-Visa-Program' of the US State Department intended for academic researchers.[113] Eventually, the institute hosted the internationally renowned scientist and Nobel Laureate Severo Ochoa. He came in 1974 and directed a research program at the RIMB until 1985. By the mid 1980s, the RIMB had seven members of the US National Academy of Science on its staff.[114]

In one instance, the RIMB even blurred the borders between Roche and the academic biological community to such a degree that it resulted in a lawsuit. In 1980, the University of California accused Roche of exploiting a cell line sampled from the bones of a patient in a Los Angeles hospital. This cell line had been important for the isolation of the interferon gene that enabled the biotech company Genentech in cooperation with the RIMB and the Roche industrial laboratories to produce the human recombinant interferon mentioned previously. In the early 1980s it was estimated that the annual sales of this protein would reach 3 billion US

111 Roche Institute of Molecular Biology, *Annual Report*, 1969 et seqq.

112 HAR FE.0.4 – 101129 c: Minutes of the RRMG meeting, 1969, typescript entitled 'RRMG 1969', p. 5.

113 HAR FE.0.4 – 101129 c: Minutes of the RRMG meeting, 11.–16.6.1970, p. 2 and Minutes of the RRMG meeting, 10.–15.6.1971, p. 5; Peyer, *Roche*, p. 226.

114 Weissbach, 'Reflections on the Roche Institute of Molecular Biology', p. 248; Udenfriend, 'A Short History', p. 280.

dollars in forthcoming years. Even though the University of California had not patented the cell line, it claimed that 'Roche "subverted" for profit the academic relationship' through which the cellular material was freely passed over to the RIMB. Robert Gallo, working for the US National Cancer Institute had given the cell line to Sydney Pestka who was in charge of interferon research at the RIMB. When the conflict between the University of California and Roche broke out, Gallo testified that he had regarded Pestka 'as a friend and researcher working at a non-profit institution, not as a corporation scientist'.[115]

Even though the RIMB was granted academic liberties, its researchers did not work in complete isolation from the rest of the company. At first, interactions between the institute's staff and the company researchers were only limited. Arnold Brossi, head of Chemistry at Roche Nutley, was rather sceptical about the usefulness of the RIMB. He seems to have been convinced that 'Roche was a successful company that had built its reputation primarily on the strength of its chemical division' and therefore 'questioned why the company should make a major financial commitment to an entirely new field that had no apparent relevance or products in mind'.[116] The senior researchers at Nutley were especially unconvinced about the RIMB. Nevertheless, closer contacts between the RIMB and the other research laboratories of Roche were eventually established, and a number of common research programs were launched.[117] To what extent Roche finally benefited from the research activities pursued at the RIMB cannot be evaluated here. But clearly, the new institute represented an important step in Roche's transition towards biological research strategies, allowing for frequent contacts between faculty in academia and industrial scientists at Roche, and towards the creation of collaborative networks in the biological sciences, similar to those which had existed for decades in the field of chemistry. The creation of the RIMB in 1967 thus contributed to blurring

115 N. Wade, 'University and Drug Firm Battle over Billion-Dollar Gene', *Science*, 209 (1980): 1492–1494.

116 Weissbach, 'Reflections on the Roche Institute of Molecular Biology', pp. 245–246.

117 HAR FE.0.4 – 101129 c: Minutes of the RRMB meeting, 11.–16.6.1970, p. 2; cf. also the annual reports of the Roche Institute of Molecular Biology.

the boundaries between academic and industrial research which has meanwhile become a dominant feature of contemporary biotechnology.[118]

'Long Range Planning'

The shift towards more fundamental biological research at Roche was not only the result of a perceived need by the Roche management for new knowledge to develop drugs, to answer regulatory needs or to connect with academic researchers. This shift also took place within a broader change in management culture at the Roche Research Management Group. Indeed, the RRMG was widening its time horizon and was consequently increasingly ready to consider investments in research whose outcome was hardly predictable. New theories of management that were emerging at the same time further reinforced this changing emphasis in research planning at Roche.

In the late 1950s, the opening remarks of the RRMG meetings still reflected a clear emphasis on short-term issues and the need to achieve rapidly commercially valuable research results. This urgency was partly due to the fact that the profits from vitamins had decreased after the Second World War and that Roche's growth rate threatened to fall behind that of its competitors.[119] On the other hand, Roche's emphasis on short-term research goals was a quite common strategy within the pharmaceutical industry at the time. According to an economic survey published in 1965 and relying on interviews with managers of pharmaceutical companies in the United States, research in this sector was not undertaken 'merely with the hope of

118 R. Loeppky, *Encoding Capital: the political economy of the Human Genome Project* (New York and London: Routlege, 2005), pp. 149–160.

119 See HAR FE.0.4 – 101129 a: Minutes of the RRMG meetings, 15.–23.10.1956, p. 1, and 24.–30.4.1957, add. to p. 1. The prize for 1 kilogram Vitamin C declined from 1140.– Swiss francs in 1936 to 102.– Swiss francs in 1950. Peyer, *Roche*, p. 175, 180 and 205.

some distant but unknown returns, but rather with the expectation that profitable gains will accrue within a reasonable period of time'.[120]

But this perspective was about to change. In 1960s, Placidius A. Plattner opened the RRMG annual meeting by saying:

> Since we are now in the fortunate position of having several promising substances as candidates for launching, the Group is able to devote more of its time to consideration of long range aspects.[121]

Plattner was referring to Roche's new benzodiazepine tranquilizer Librium; now that new drugs were ready for market, he considered it important to spend more time discussing long-term agendas.[122] The financial situation of the company further improved throughout the following decade, and by 1967 Roche had become the world's largest pharmaceutical company in terms of sales.[123] This favourable economic position made it possible to integrate long-term planning with the management of scientific research within the company, and by the mid 1960s, Roche Nutley had established an independent committee in charge of 'long range planning' within its research department.

According to the editorial of the first issue of the eponymous journal, 'long range planning' was neither a single technique nor a specific managerial strategy, but was aimed at 'developing attitudes, processes, and perspectives which make planning possible'.[124]

120 W.S. Comanor, 'Research and technical change in the pharmaceutical industry', *The Review of Economics and Statistics*, 47 (1965): 182–190 (190).

121 HAR FE.0.4 – 101129 a: Minutes of the RRMG meeting, 25.–30.4.1960, p. 1.

122 Cf. also HAR FE.0.4 – 101129 a: Placidus A. Plattner to the Roche Head Office, 9.5.1960.

123 Peyer, *Roche*, p. 213.

124 R. Perrin, 'Long Range Planning: the concept and the need', *Long Range Planning,* 1 (1968): 3–6 (5).

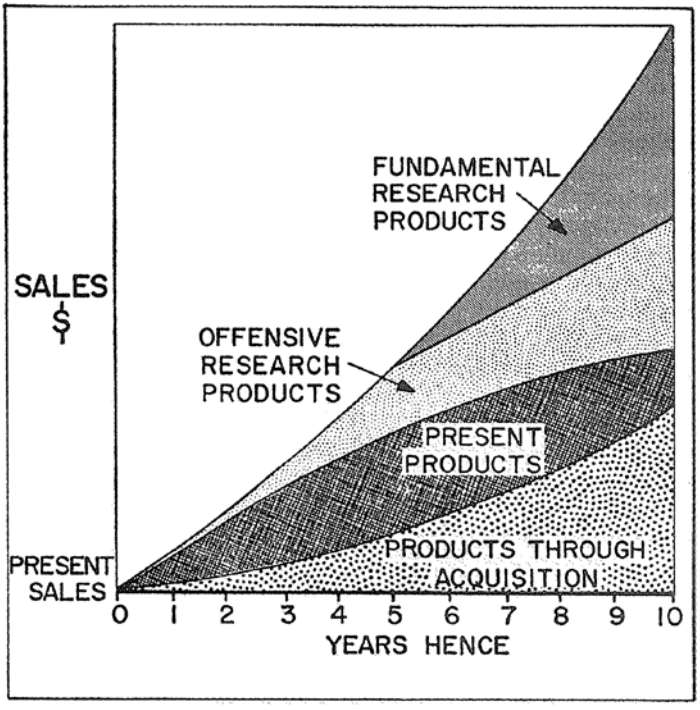

FIG. 1

Fig. 4. Chart from a management guide for long range research planning illustrating the need for fundamental research programs in industry, 1964.[125]

As far as managerial attitudes were concerned, the concept of 'long range planning' was first of all a plea to take entrepreneurial risks, i.e. to plan the future even though it could never be properly predicted. Up to that point, unpredictability had been one of the key reasons why management had refrained from tackling issues beyond short-term planning.[126]

125 J.B. Quinn, 'Top-Management guides for Research Planning', in D.W. Ewing (ed.), *Long Range Planning for Management* (York etc.: Harper & Row, 1964), pp. 262–296 (385).

126 P.F. Drucker, 'Long Range Planning Means Risk-Taking', in Ewing (ed.), *Long Range Planning for Management*, pp. 7–20. On Drucker and management science, see S.P.

A first comprehensive reader for managers on 'long range planning' had appeared in 1958. The second edition, published in 1964, contained an article on 'Top-Management Guides for Research Planning' written by James B. Quinn, professor of Business Administration at Dartmouth College. According to Quinn, the main purpose of research planning was to define the kind of research a company needed in order to achieve its long-term goals. He distinguished among three different kinds of research projects. In the first two instances, they could aim at defending products a company was already selling, or they could serve to develop foreseeable new products. Both of these approaches could be carried out with a high probability of success, but they might not enable the company to meet its economic goals. In order to do so, a company might need a third 'technology, which develops entirely new applications beyond the scope of those presently foreseen'. In these cases, Quinn argued, a fundamental research program was necessary even though its outcome could hardly be predicted.[127] The plea to take risks, which was a constitutive element of the concept of 'long range planning', was therefore also an argument in favour of fundamental research (Fig. 5). The RRMG members learned more about this new management perspective in 1967, when an expert from Roche Nutley presented the concept of 'long range planning' in more detail and distributed scientific papers from the Harvard Business School on that subject.[128] By that time, a number of corporations had already established formal long range planning departments, and the Roche management itself considered the company's rising investments in fundamental research well in tune with this general trend towards long-term planning in corporate management.[129]

Waring, *Taylorism Transformed: Scientifc Management Theory since 1945* (Chapel Hill and London: University of North Carolina Press, 1991).

127 Quinn, 'Top-Management Guides for Research Planning', p. 386.

128 HAR FE.0.4 – 101129 b: Minutes of the RRMG meeting, 18.–23.5.1967, typescript entitled 'RRMG 1967', pp. 67–68.

129 'Auszug aus der Präsdidialadresse von Dr A.W. Jann, 10. Juni 1966'. *Roche Nachrichten* No. 3 (1966), without pagination; cf. also L.R. Michel, 'Long range Planning for Management', *Management Science*, 11, Series A, Sciences (1964): 210–211.

Conclusion

In his recent book on the history of twentieth century pharmaceutical industry, business historian Alfred D. Chandler Jr. traces Roche's position today back to what he calls the company's 'aggressive entry into the new biotechnology'[130] in the 1980s. Our investigation into the Roche Research Management Group (RRMG) during the two previous decades allows us to qualify this picture. The RRMG appears as an institutionalized place within the company where, even in the 1960s, the potentials of different scientific approaches to drug development were evaluated, legal constraints were interpreted, and future technological as well as institutional needs were determined. In this context, Roche decided to reorient its research priorities towards increased fundamental biological research. Thus, when Roche entered the new biotechnology in the 1980s, whether 'aggressively' or not, it had already undergone a major scientific and institutional transition towards a biological mode of drug innovation.

In this paper, we have tried to demonstrate how and why the management and the researchers at Roche began reassessing the company's traditional approach to drug development based on organic synthesis and a reliance on close relationships with chemistry departments in academia. We have argued that four main factors explain why the company adopted a new approach to drug development, aimed at understanding the molecular mechanisms of drug action and identifying the precise biological targets of drugs. First, the previous chemical approaches were criticized by managers and scientists because of decreasing results, opening the door for claims that fundamental biological knowledge would allow for more productive modes of drug development. Second, the tightened FDA drug approval policies required more profound pre-clinical knowledge on the mechanism of action of drugs, which could be provided by biological research. In addition, the increased costs of clinical trials made it even more important to carefully evaluate the chances of success at an early pre-clinical stage. Third, given

130 Chandler, *Shaping the Industrial Century*, p. 258.

that Roche had decided to emphasize biological research, it focused particularly on fundamental research as a means to attract academic scientists and overcome its isolation from the academic biological research community. And finally, having adopted the new principles of long range planning and accepted the risks inherent to planning an unpredictable future, the management was ready to consider investments in fundamental biological research even though its economic value was still unforeseeable.

The link between the transition undergone by Roche in the 1960s and the biotechnology era still remains to be explored. How important, for example, was Roche's new in-house biological expertise when recombinant DNA technologies became available and opportunities emerged to collaborate with biotech start-ups? The RIMB might have played an important role in that respect. Roche monitored advances in molecular genetics attentively through its researchers at the RIMB and their close contacts with the academic molecular biology community. In the late 1970s, the RIMB also served as an interface between Roche and the new biotech start-ups such as Genentech, with which Roche scientists collaborated for the isolation of the interferon gene, before Roche acquired Genentech in 1990.

Besides the links to contemporary biotechnology, another area which requires more investigation is clinical research. In retrospect it has become clear that the new FDA laws and regulations of the early 1960s had a major impact on clinical research. It is therefore surprising how little the Roche management and scientists discussed a reconfiguration of the company's relationships with clinics and physicians – at least in the sample of sources this article is based upon. In the discussions we outlined, improving clinical research was not considered an alternative way to overcome problems in developing new marketable compounds. More archival research would be needed in order to evaluate what importance clinical research had for the Roche management when it was confronted with the various problems outlined in this article.

Other important aspects still need further investigation. As far as Roche is concerned, more attention could be paid to the impact of the new generation of managers on the company's research strategies, and in particular of the American managers who started to fill top positions

traditionally occupied by Swiss executives. Such a trans-national perspective could be further explored by a comparison of Roche with other companies, for instance the Swiss-based Ciba, which was considerably less engaged in the United States than Roche until the 1970s, or the large American pharmaceutical companies which had acquired more experience with biological research than had Swiss and German companies during the inter-war period.[131] A trans-national perspective is also essential to address more carefully the impact of the social, economic and especially legal environments on pharmaceutical research, which we could only cover briefly. Drug patent laws, drug safety regulations, and drug advertisement limitations constitute powerful forces that shape the opportunities for drug development. In addition to examining the contexts of pharmaceutical activities, another topic that remains to be explored are the links between the industry's search for biological targets for new drugs and the earlier practices of biological research, in particular biological screening, toxicological research, and the improvement of biological production methods. This century-old biological expertise might have constituted important material, intellectual and institutional resources when pharmaceutical companies embarked upon fundamental biological research on a larger scale in the 1960s.

Finally, this case study raises new questions about the periodization of the transformation of the pharmaceutical industry in the twentieth century. Our paper suggests that the introduction of a new research strategy – starting from the (biological) target, not the (chemical) bullet – constituted an important transition for the management and for the scientists at Roche. This perspective, taking into account the management, scientific, as well as institutional practices, opens a middle ground between the *longue durée* of biotechnology as a way to exploit living processes industrially, and the short-term accounts of the 'biotech revolution' centred on the introduction of recombinant DNA technologies.[132]

131 Swann, *Academic Scientists and the Pharmaceutical Industry*.

132 For a similar account see J.-P. Gaudillière, 'Introduction: Drug Trajectories.' *Studies in History and Philosophy of Biological and Biomedical Sciences*, 36 (2005): 603–611.