RECOLLECTIONS

First steps in peptide science

ROBERT SCHWYZER

Laboratory of Molecular Biology and Biophysics, Swiss Federal Institute of Technology, CH-8093 Zürich, Switzerland

Mary McCarthy, in her *Memories of a Catholic Girlhood*, describes a major difficulty in writing recollections: events that seemed very clear in her mind had, according to others, happened in a rather different manner. I wish, therefore, to caution the reader that the present recollections may be prone to similar fallacies, even though I have tried my best to avoid them in both the factual and anecdotal sections. Intended as an homage to bygone teachers and mentors of yesterday, they pay only cursory or no attention to living friends and colleagues. I ask forgiveness of the reader who, for that reason, should feel slighted.

Reprint requests to: Robert Schwyzzer, ETH, Hartriegelstrasse 12, CH-8180 Bülach, Switzerland.

Robert Schwyzzer went to school in Minneapolis, Minnesota, and returned to Switzerland with his parents at the age of 13. He graduated from the University of Zürich with a dissertation in organic chemistry (Professor Paul Karrer) on "Vitamins and Antivitamins" (1947) and was promoted to "Privat-dozent" in 1951 for work on the synthesis of folic acid, pteridines, and other natural products. He then led a research group at the Chemistry Department of the University of Zürich and founded the Peptide Research group of CIBA Ltd., Basel, in 1952. Those positions were given up in 1963, when he was asked to join the Swiss Federal Institute of Technology (ETH) in Zürich as founding chairman and professor of Molecular Biology and Biophysics. He was a visiting scientist at the Biochemistry Department of the University of Helsinki, Finland, with Artturi I. Virtanen (1950), at the Hormone Research Laboratory of the University of California, Berkeley, with Choh-Hao Li (1958), and at the Department of Biochemistry, University of Washington, with Hans Neurath in 1964 (Senior Foreign Scientist Fellowship of the National Science Foundation). From 1952 to 1963, his research on the synthesis of bioactive peptides was sponsored by CIBA. Since 1963, his work centered on peptide structure–activity relationships and the molecular mechanism of receptor discrimination, and was supported mainly by grants from the Swiss National Science Foundation and the ETH.

Dr. Schwyzzer was a guest professor at different Universities in the USA and is now Professor in Residence at the Clinical Research Institute of Montreal. Numerous international awards and medals, including The Scheele Lecture, Stockholm, 1963 (Message–Address Concept of Structure–Activity Relationships); the Otto Naegele Prize, Switzerland, 1964 (First Synthesis of ACTH); the Stouffer Prize, Cleveland, Ohio, 1968 (Synthesis of Angiotensin); the Paul Karrer Lecture and Medal, 1969 (Programmed Molecules); the Ernesto Scoffone Memorial Lecture, Gold Medal of the Università degli studi di Padova, Italia (Peptide–Membrane Interactions); Alan E. Pierce Award and Lecture, American Peptide Symposium, Toronto, 1985 (Peptide–Membrane Interactions); the Josef Rudinger Memorial Lecture and Award, European Peptide Symposium, Porto Carras, Greece, 1986 (Membrane Compartments Theory of Receptor Subtype Selection). He is a member of the Deutsche Akademie der Naturforscher, Leopoldina, and an honorary member of the Advisory Council of the American Heart Association and of the American Peptide Society.

Academic freedom

In 1951, as a young Privatdozent in Zürich, I asked my teacher, Professor Paul Karrer (1889–1971; Nobel Laureate in chemistry, 1937), whether I might—on a side line to my work with vitamins, bitter principles, alkaloids, and pteridines—start experiments in peptide chemistry. I was fascinated by the early papers of Frederick Sanger on the degradation of insulin that had just appeared, and was convinced that peptides and proteins were a great new challenge for organic chemists. Karrer replied, no, it was much too early, and the time not yet ripe. A respected authority, 62, thin, frail, low-voiced, shy, and therefore carefully keeping his distance to others, he was revered by the few able to see behind his protective mask, but was shunned and even feared by others. I understood that he did not want me, his employee, to open a field of my own.

I should like to remind the reader that, during my previous work, most methods that are matter-of-course today were still unknown. UV spectroscopy was done at a pace of about one spectrum a week by photography of iron spark spectra and comparing the intensities of the iron spectral lines obtained with or without intervening solutions of the compound to be measured. I remember unpacking Karrer's first Beckman Uvicord in 1949—what a relief! Visual spectroscopy of carotenoids, which had been isolated from alumina or calcium hydroxide columns after development with petroleum ether, was done with a simple prism mounted in the beam of an incandescent lamp, and the line pattern was interpreted as structure in a quite intuitive manner, for which Karrer was an expert. Paper chromatography (Martin and Synge), separation of amino acids on potato starch columns (Stein and Moore), and counter-current distribution (Lyman Craig) were godsend when they appeared. Thin-layer and reversed-phase high-pressure chromatography were not yet available, neither were the IR and NMR techniques necessary for conformational analysis.

In that same year of 1951, I was invited to spend three months in Helsinki, Finland, with my wife, where I worked with Professor Artturi Ilmari Virtanen, Biochemist and Nobel Laureate (1945). Virtanen was quite the opposite to Karrer. His size, strong voice, and hearty manner restored a good deal of self-confidence in this young couple, particularly because Artturi announced that it is never too late for a second honeymoon, and packed us off to an experimental station 500 km north of Rovaniemi, which we reached by DC-3 from an unprepared runway, and by bus and row boat in a sweltering heat and clouds of mosquitoes. Back in Helsinki, we slept in the laboratory on cots, and ate sour milk, boiled potatoes,

Fig. 1. Professor Paul Karrer, delivering his chemistry course for medical students at the University of Zürich. The year is about 1945. Although he was at first quite skeptical, he later strongly supported peptide chemistry by allotting me ample space for research and teaching in his institute, even during the period of my industrial employment (1952–1963).

fish, and berries—the daily food of the poverty-stricken austere Finns, five years after the war. (My wife remembers the daughter of Finland's President Paasikivi throwing a party with just two oranges—given her by a diplomat—and dividing them in small morsels among the participants.)

Virtanen was interested in the uptake of amines through the roots of plants, and we decided to study peas and analyze the sap with the recently described method of paper chromatography. The results were published in *Acta Chimica Scandinavica* and reassured me in my intention to study peptides. Artturi and his wife remained very close friends of our young family, and visited whenever they came to our country.

Toward the end of 1951, in Zürich, Dr. Carlo Miescher, Director of the Pharmaceutical Department at CIBA Ltd., came to visit me. He had seen my recent papers and now asked me to join his group in Basel. Steroid hormones and antibiotics were in the focus of interest at CIBA. He said I could choose my own field of research. When asked about peptides, he said he had no idea what they were good for, but, if I thought them worthwhile and profitable, I was welcome to go ahead. So, in 1952, I joined CIBA, but kept my teaching position and my doctorate students in Zürich.

Fig. 2. The author at the time of his formal retirement (1988).

A first try at peptide synthesis

At that time, glutathione was the choice target of at least 10 “peptide” groups in Europe. Everybody was after glutathione, the structure of which had been elucidated in 1929–1930 (Hopkins; Kendall). However, an antibiotic, gramicidin S, had been isolated in the Soviet Union and its structure elucidated between 1945 and 1951 in the laboratories of R.L.M. Synge, F. Sanger, and L.C. Craig as cyclo-(Val-Orn-Leu-D-Phe-Pro)₂ (Table 1). Recent attempts at its synthesis in at least three laboratories had failed because no suitable method for ring closure was available. I decided to have a try, but first had to invent new synthetic methods.

Paper chromatography and simple counter-current purification with a battery of 10 separatory funnels helped in the first synthesis of crystalline *S*-acyl derivatives of pantetheine, which I wanted to use as models for peptide bond formation under aqueous, so-called “biological” conditions. From experiments with activation by metal ions (Ag⁺; Pb⁺⁺), I developed the concept of “activated esters” (1954): amino acid and peptide esters containing electron-attracting groups in the alcoholic moiety, e.g., esters of cyanoethanol, *p*-methanesulfonylphenol, and *p*-nitrophenol. Such esters were prepared readily from (protected) amino acid or peptide carboxylate salts and cyanomethylchloride or the (substituted) phenylsulfites. My friend, the late Theodor Wieland in Heidelberg, was—at the same time—pursuing the thioester and mixed anhydride methods, and Miklos Bodánszky published experiments with *p*-nitrophenylesters prepared from amino acid chlorides or anhydrides and the phenol.

A first highlight was the successful synthesis of the cyclic decapeptide antibiotic, gramicidin S, cyclo-(Val-Orn-Leu-D-Phe-Pro)₂, from the linear decapeptide *p*-nitrophenylester or *p*-methanesulfonylphenylester (Table 2), performed together with my lab technician, Peter Sieber. Attempts to cyclize the pentapeptide moiety alone quite unexpectedly yielded not the cyclic pentapeptide, but substantial amounts of the cyclic decapeptide: this fact caused me to speculate about possible secondary structures. A short antiparallel pleated sheet joined by two β -turns, quite a novelty at that time, explained the observed phenomena. A few weeks after my first lecture on the subject, the late Professor Leopold Ruzicka,

Table 1. *Natural peptides elucidated 1945–1964*

#	Year	Peptide structure elucidated	Group, authors
01	1945	Gramicidin S cyclodecapeptide	Synge
02	1952	Tyrocidin A cyclodecapeptide	Battersby, Craig.
03	1953	Vasopressins (Lys, Arg) nonapeptides	Acher, Chauvet
04	1953	Oxytocin nonapeptide	Tuppy
05	1953	Oxytocin nonapeptide	du Vigneaud et al.
06	1954	Vasopressins (Lys, Arg) nonapeptides	du Vigneaud
07	1954	ACTH nonatriacontapeptide, pig	Bell (Am. Cyanamide)
08	1955	Tyrocidins B,C cyclodecapeptides	King, Craig
09	1955	ACTH nonatriacontapeptide, sheep	Li, C.H. et al.
10	1956	β -MSH octadecapeptide	Geschwind et al.
11	1956	β -MSH octadecapeptide	Harris, Roos
12	1956	α -MSH ac-tridecapeptide-amide	Lee, Lerner
13	1956	[Ile ⁵]-Angiotensins I, II, equine	Skeggs et al.
14	1956	[Val ⁵]-Angiotensin I, bovine	Elliott, Peart
15	1956	Glucagon nonacosapeptide	Bromer et al.
16	1958	Eolidin cycloheptapeptide	Law et al.
17	1960	Bradykinin nonapeptide	Boissonnas et al.
18	1960	Fungisporin cyclo-octapeptide	Miyao
19	1962	Eledoisin undecapeptide	Erspamer, Anastasi
20	1962	Bacitracin F branched cyclohexapeptide	Konigsberg, Craig
21	1964	Gastrin I, II heptadecapeptide	Gregory et al.
22	1964	Polymyxin B1 IpeI-(7 α -decapeptide)	Vogler et al.

Nobel Laureate (1939) and Head of the Laboratory of Organic Chemistry of the ETH, summoned me to his home one afternoon. Shortly after my arrival, Dorothy Crowfoot Hodgkin (the late Nobel Laureate, 1964)—who was to become a dear friend—appeared on the scene. I explained my ideas about the conformation of gramicidin S. Dorothy then got up, went to her car, and returned with a huge cardboard box. From it she took a big wire model, which looked exactly like the small one I had brought from Basel. Her model represented the most probable conformer among those fitting her X-ray diffraction data. A surprise meeting, beautifully staged by the ever witty Ruzicka. (The suggested conformation, with its twofold axis of symmetry, was confirmed by NMR [Schwyzer; Craig, 1968] and molecular modeling [Scheraga, 1969]).

Having heard of my work, Choh Hao Li, then Head of the Hormone Research Laboratory of the University of California at Berkeley, came to visit me in Basel to learn about peptide synthesis. He soon decided that he needed more instruction and invited me to Berkeley to teach peptide chemistry. This I did in the summer of 1958, and synthesized an active pentapeptide subunit of α -MSH (α -melanotropin). The visit was repeated in 1959, when I gave free advice on the synthesis of long-chain ACTH peptides. During those visits to the USA, I made many new friends, among them Vincent du Vigneaud (who gave me his book: *A Trail of Research*, Cornell 1952, “as a little memento after a delightful seminar”), Melvin Calvin, Robert Burns Woodward, Linus Pauling, Lyman Craig, John Edsall, Joe Fruton, George Némethy, Harold Scheraga, and Hans Neurath.

Peptides 1952–1963

During my time at CIBA Ltd. (1952–1963), about two dozen structures of biologically active peptides were published (Table 1). They were interesting candidates for synthesis. Because my work

was going well, a peptide research group was founded, and I recruited a number of excellent research chemists as coworkers: Beat Iselin, Werner Rittel, Bernhard Riniker, Heinrich Kappeler, Peter Sieber, and Herbert Zuber, complemented by Max Feurer and Boris Gorup in the pilot and production plants. Most of them had just completed postdoctoral training in the USA with scientists such as Karl Djerassi, Erwin Chargaff, Klaus Hofmann, and—in Germany—with Helmut Zahn.

It was a stimulating experience to realize how other groups were also beginning to work in the field, both analytically and synthetically. Because they came from a predominantly chemical background, they were convinced that a synthesis must provide independent proof of structure in order to be acceptable. Thus, larger peptides were built from well-characterized smaller ones (fragment condensation) or even by adding one amino acid residue after another, all the while purifying and characterizing the intermediates. Many therefore kept a skeptical eye on the ingenious solid phase method described in 1964 by Merrifield (Nobel Laureate 1984) that could not, per se, provide such a proof, but depended on the often difficult separation and structural elucidation of the end products. However, with further technical developments in separation and analysis, and its automation, it is today regarded as the method of choice, particularly because it allows the preparation of large “peptide libraries” from which to choose those individuals with the required properties. Fragment condensation has been kept alive, though, particularly in Japan, to solve industrial large-scale problems and to synthesize proteins (e.g., ribonuclease A by Fujii & Yajima, 1981, and at least 17 others with 20–130 amino acid residues, including rat interleukin-8, parathyroid hormone, and angiogenin by Shumpei Sakakibara, 1980–1995).

In 1953, the news of Vincent du Vigneaud’s breakthrough with oxytocin and vasopressin (Table 2) was a great stimulus for all.

Table 2. *Natural peptides synthesized 1953–1963*

#	Year	Peptide synthesized	Group, authors
01	1953	Oxytocin nonapeptide	du Vigneaud
02	1954	[Lys ⁸]-vasopressin nonapeptide	du Vigneaud
03	1954	[Arg ⁸]-vasopressin nonapeptide	du Vigneaud
04	1956	Gramicidin S cyclodecapeptide	CIBA Schwyzer, Sieber
05	1957	[Ile ⁵]-Angiotensin II octapeptide	CIBA Rittel et al.
06	1957	[Ile ⁵]-Angiotensin II octapeptide	Schwarz, Bumpus, Page
07	1958	α -MSH acetyl tridecapeptide amide	SANDOZ Boissonnas et al.
08	1958	[Val ⁵]-Angiotensin I decapeptide	CIBA Schwyzer et al.
09	1958	[Val ⁵]-Angiotensin II octapeptide	CIBA Schwyzer et al.
10	1958	[Ile ⁵]-Angiotensinogen tetradecapeptide	Skeggs et al.
11	1959	Phalloidin partial heptapeptide sequence	Wieland et al.
12	1960	Bradykinin nonapeptide	SANDOZ Boissonnas et al.
13	1960	ACTH (1–23)	Hofmann et al.
14	1961	ACTH (1–24)	CIBA Schwyzer, Kappeler
15	1962	Isotocin nonapeptide	SANDOZ Guttman et al.
16	1962	Kallidin decapeptide	SANDOZ Pless et al.
17	1962	Eledoisin undecapeptide	SANDOZ Sandrin et al.
18	1962	Sporidesmolide I cyclohexapeptide/-olide	Shemyakin et al.
19	1963	Valinomycin cyclododecapeptide/-olide	Shemyakin et al.
20	1963	Enniatin B cyclohexapeptide/-olide	ROCHE Plattner et al.
21	1963	α -MSH acetyl tridecapeptide amide	CIBA Schwyzer et al.
22	1963	β -MSH octadecapeptide	CIBA Schwyzer et al.
23	1963	ACTH (1–39)	CIBA Schwyzer, Sieber
24	1963	Insulin A (henikosa)+B (triakonta)	Meienhofer, Zahn et al.
25	1963	Insulin A (henikosa)+B (triakonta)	Niu, Kung et al.
26	1964	Gastrin heptadecapeptide	Kenner et al.
27	1964	Polymyxin B1 acyl cyclo-7 α -decapeptide	ROCHE Vogler et al.

Many groups in Europe now turned from glutathione to the study of (modified) syntheses of oxytocin and vasopressin. However, a small number aimed at other targets. Much of the pioneer work was done in Europe and in Swiss pharmaceutical companies, e.g., CIBA, ROCHE, SANDOZ, and GEIGY. At times, the competition became quite hot. Most work was published in French or German. At that time, many English speaking chemists were fluent in those languages, allowing for a sufficiently rapid and broad dissemination of the news. Toward the end of the decade, things changed, and one had to publish in English in order to be read.

New peptides and products of importance from my own group were [Val⁵]-angiotensin (Hypertensin CIBA), α -melanotropin, β -melanotropin, and corticotropin-(1–24)-tetracosipeptide (CIBACTHEN) in kilogram quantities. The syntheses were performed in solution, care being taken to isolate, purify, and chemically characterize all intermediates, in order to prove the structure independently of amino acid sequence analysis. For this purpose, new side-chain protecting groups were developed that could be removed without destroying even sensitive peptides. Activated esters, mixed anhydrides, azides, and dicyclohexyl-carbodiimide (Gobind Khorana; John Sheehan) were used for condensation. The total synthesis of corticotropin-(1–39)-nonatriacontapeptide (ACTH) with Peter Sieber completed the series (1963). It was first announced at a seminar of the CIBA pharmaceutical research department, at which Bob Woodward attended—I remember him getting up to applaud.

[Val⁵]-angiotensin (Hypertensin CIBA®) was first used in the treatment of wound shock, but was soon replaced by infusion techniques. Its main importance lay in its worldwide distribution to

hypertension research laboratories for promoting knowledge that led to new antihypertensive drugs (e.g., inhibitors of angiotensin converting enzyme and renin). Corticotropin-(1–24)-tetracosipeptide (CIBACTHEN) is an ACTH substitute lacking the allergic effects caused by impurities in ACTH preparations isolated from pituitaries.

A spectacular synthesis of gastrin heptadecapeptide was accomplished in 1964 by my late friend George Kenner in Liverpool, and the structure of the cyclic, branched antibiotic polymyxin B1 was proved by my deceased friend, Karl Vogler (ROCHE). In 1963–1964, the total syntheses of the insulin A and B chains and their random oxidative recombination to crystalline insulin were announced in China by my friends, the late Ching-I Niu and Yue-ting Kung (now Gong), in Germany by the group of Helmut Zahn, and in the USA by Katsoyannis. A synthesis that truly proved the topology of the three disulfide bonds, however, had to await the very sophisticated differential protection of the six cysteine residues and the stepwise formation of the disulfide bonds by my former CIBA group (1974–1977; Werner Rittel et al., supplemented by the GEIGY group, Bruno Kamber et al.).

Structure–activity relationships

The pharmaceutical orientation of many groups doing peptide synthesis produced a host of analogues with amino acid sequences different from those of the natural products. Correlations between primary structures and biological properties were examined in order to find rules for the rational prediction of quantitative structure–activity relationships (QSAR). I became fascinated by the analogy between peptide structure, with its 20 amino acid residues, and our

written language with as many letters and, since 1962, laid the foundations for the now well-known "Message-Address" and "Membrane Compartments" theories of peptide QSAR. They have been widely accepted and—*mutatis mutandis*—extended to immunochemistry and even compounds other than peptides, e.g., opiate alkaloids (Portoghese, 1989). The ideas were developed—experimentally and conceptually—between 1962 and 1995, and gradually replaced my interest for peptide synthesis.

Message-address theory

Many biologically active peptides are found to occur in structurally related families and to contain continuous segments of amino acid residues similar to words in a written sentence, each one spelling out a different component of the total information. Thus, the *message* is held responsible for triggering all the receptors for a given peptide family (e.g., for melanocortin or opioid peptides), but the *address* directs the message to the individual receptor subtypes (e.g., to μ -, δ -, or κ -opioid receptors). Within a family, messages are conserved and addresses are variable—so much so, that it is often impossible to associate the amino acid sequences of the addresses with receptor subtype selection. In many cases, the variability even seems to rule out specific binding as the selection mechanism. How, then, does the address work? Does it influence message conformation?

Membrane compartments theory

Our early experiments with NMR suggested that cyclic peptides (e.g. hexapeptides, decapeptides) are folded and occupy a restricted conformational space (with Aung Tun-Kyi, 1964). Other experiments with fluorescence depolarization and intramolecular nonradiative energy transfer, by my doctorate student, Peter Schiller (1970), indicated that bioactive peptides are flexible and occupy a large conformational space. Later studies using IR attenuated total reflection spectroscopy, membrane capacitance minimization, and other suitable methods revealed specific interactions of flexible peptides with lipid bilayer membranes that correlated well with receptor selection (work together with David Sargent, Hans-Ulrich Gremlich, Shunsaku Kimura, Daniel Erne, and many doctoral students, 1979–1987). Depending on the bulk physical properties of the address, the message appeared either to remain preferentially in the aqueous phase, to be accumulated electrostatically on the membrane surface, or to be oriented perpendicularly as an α -helix in the hydrophobic surface gradient of the membrane. In 1986, I found that the observed type of message-membrane interaction can be predicted exactly from the amino acid sequence of the peptide and correlated quantitatively with receptor selectivity and binding strength. The derived "Membrane Compartments Theory of Receptor Subtype Selection" provided for the first time a means for predicting receptor subtype selectivity of peptides (Schwyzer, 1985–1995).

Changes

One fine morning in 1960, I was summoned to the office of the new director of the pharmaceutical department of CIBA. Dr. Albert Wettstein, renowned for his steroid work, particularly syntheses of cortisone and cortisol, shook his head in mock reproval and greeted me with the words: "Doctor Schwyzer, you are an odd fellow: almost every one of my research chemists comes around to my office every two or three weeks to ask for a promotion, but I never had you here before. Nevertheless, the board of directors wishes to promote you to Vice Director."

This was meant to be the beginning of an industrial career, and the next step was announced two years later. This time, I felt uneasy about the development and was afraid of becoming an administrator, just promoting my old products and managing research and sales. Fortunately, I was able to decline, because I had been offered positions by a number of academic institutions in the USA, Germany, and Switzerland. The most appealing offer—personally, scientifically, and geographically—came from Hans Neurath, Head of Biochemistry at the University of Washington in Seattle. However, I was under strong moral pressure to remain in Switzerland, where I accepted a position as founding director of the Laboratory of Molecular Biology and Biophysics on the Physics Campus of the Swiss Federal Institute of Technology (ETH) in Zürich. I was very concerned about turning Hans Neurath down. But he was extremely gracious and acted as a true friend, not only by understanding my motives, but by inviting me to spend a year in his department with a Fellowship of the National Science Foundation, which helped bridge my transition from Basel to Zürich. With my family and two of my coworkers, I spent an extremely stimulating year in Seattle. Good science, hiking, and skiing with Hans and his wife, Susi—a lasting memory for my family and me.

To Dr. Wettstein I am still grateful for his continuing friendliness during and after the transition—he was later to die under very tragic circumstances.

Academia again

Preparations for a new Laboratory of Molecular Biology and Biophysics were made with the President of the ETH, Professor Pallmann. Molecular Biology was defined as structural biology on a molecular scale. It was meant to include relationships between peptide biological activity and structure. In order to broaden the scope, I asked my former coworker, Dr. Herbert Zuber, to join me, because he was an expert with proteins and primary structure determination. Our first laboratory was a temporary, barracks-like structure in the entrance court to the chemistry department of the ETH (Bob Woodward used to throw pebbles at my window before entering). During this phase, I was joined by a postdoctoral associate with experience in NMR, Kurt Wüthrich. For lack of space, he worked in the nearby Laboratory of Physical Chemistry of the ETH, close to Richard Ernst, the NMR specialist and later Nobel Laureate. Another acquisition was Josef Rudinger, who had led the peptide group of the Czechoslovak Academy of Sciences in Prague. Through the president of the academy, Fritz Šorm, I invited Joe to come to Zürich in 1968 because he was in danger of imprisonment for his political involvement in the "Prager Frühling" (Joe and I had known each other as members of the Joint IUB-IUPAC Nomenclature Commission).

After five years, we all moved to a new, permanent building on the premises of the Physics Department on the Hönggerberg, where we were welcomed warmly by our physicist colleagues. Unfortunately, Professor Pallmann had died before our move, but we had arranged to include a genetically oriented group at the new location. Due to the lack of funds, the ETH offered the University of Zürich space for their molecular biology lab. This was a very propitious decision, because the designated head of that group was Professor Charles Weissmann, the well-known molecular biologist, whom I knew personally since his time as a student with Paul Karrer.

Our institute developed well. Herbert Zuber, Joe Rudinger, and Kurt Wüthrich were appointed full professors. Tragically, Joe Rudinger died in 1975, at the age of only 54.

Herbert Zuber started to study thermophilic organisms and was very successful in elucidating the relationships between properties (thermophily and thermostability) and structures of thermophilic enzymes. He also established the primary structures of antennae polypeptides of cyanobacteria and photosynthetic bacteria as a foundation for X-ray diffraction by Robert Huber (Nobel Laureate) in Munich and Richard Cogdell at Glasgow, with whom he collaborated. His work involved genetic and DNA studies and culminated in the determination of the architecture of the antennae complexes and the phycobilisome. He has now retired.

Kurt Wüthrich initiated an effective NMR group that he updated continuously with most modern equipment and prime graduate students and postdoctoral fellows. We collaborated for a while on the conformation of cyclic peptides (10 papers, 1971–1976), and he was the first to develop Richard Ernst's method of two-dimensional NMR into a powerful tool for elucidating primary, secondary, and tertiary structures of proteins and of peptides with a preferred conformation. Highlights are the solution conformation of the *Escherichia coli lac* repressor DNA binding domain, the structure of the *Antennapedia* homeodomain, details of homeodomain–DNA recognition, cyclosporin and cyclophilin dynamics, protein and nucleic acid hydration in solution, work on protein folding, and, most recently, the structure determination of a self-folding prion protein domain as a step toward understanding prion diseases, such as bovine spongiform encephalitis (BSE) and Creutzfeldt–Jakob disease (CJD) in humans.

My own work concerned peptide structure–activity relationships as described above. The “Message–Address Concept” of peptide QSAR and the “Membrane Compartments Theory of Re-

ceptor Subtype Selection” have generated much discussion and experimental effort in peptide chemistry; today, their predictions seem both justified and useful for constructing peptides with specified activities.

The Institute of Molecular Biology and Biophysics at the ETH has developed into a first-rate center of structural biology, with leading groups in NMR determination of peptide, protein, and nucleic acid structures in solution. Its scope was extended with X-ray crystal structure determination (Timothy Richmond) and genetic engineering techniques (Rudi Glockshuber). Former doctoral students and postdoctoral associates are active in leading positions elsewhere. I shall mention only one from each group: Hans Hengartner (immunology, ETH and University of Zürich), Gerhard Wagner (Biological Chemistry and Molecular Pharmacology, Harvard), and Peter Schiller (Chemical Biology and Peptide Research, Clinical Research Institute of Montreal, and University of Montreal).

Further steps in peptide science

Further steps in peptide science promise to unfold the myriad wonders of that field, which has given me so much pleasure in the past. Maybe I shall even live to experience the first molecular model of a peptide agonist triggering a receptor. Luis Moroder and Horst Kessler in Munich presented strong evidence that a membrane-bound peptide message actually can enter a seven helix transmembrane receptor from the lateral membrane compartment and productively interact with the recognition site—as postulated by the “Membrane Compartments Theory.”