It all started with a chance encounter in the fall of 1935. As a second year medical student at the Catholic University of Louvain (Belgium) with time on my hands, I conformed to the local tradition according to which “good students” would “do a laboratory,” which meant that they joined the laboratory of one of their professors and participated on a voluntary basis in whatever research was going on. This arrangement suited both parties. The professors got free manpower. The students kept out of mischief, gained experience, had fun, and (if they persevered long enough) could write up a dissertation and use it to compete for a traveling fellowship. Many a scientific career was launched in this way.

Pre-war Louvain

The Physiology Laboratory—By pure chance, I became associated with the laboratory of one of the rare, true scientists on the medical faculty. He was Joseph P. Bouckaert, the professor of physiology, who, after spending 1 year in the London laboratory of A. V. Hill, winner of the 1922 Nobel prize in medicine, had, against great odds, created a modest but thriving research laboratory. Not much of a bench worker himself, Bouckaert was greatly helped by his second in command, Pierre-Paul De Nayer, a skillful and multivalent experimenter, who ran the practical classes and supervised much of the research work. Investigators enjoyed considerable freedom under this dual guidance, productively channelled by De Nayer’s technical rigor and by Bouckaert’s encyclopedic knowledge and keenly analytical mind. Particularly important especially in the academic setting of a university with strong ties to the Catholic Church (I have described this setting elsewhere (1)) were Bouckaert’s total dedication to basic research and his strong conviction that all phenomena of life had to be explained in strictly physical and chemical terms without calling on any sort of “vital force.” Without his example, I would probably never have embraced a scientific career.

Bouckaert had no pet subject. Dedicated to teaching, he had the strange idea that the research done in his laboratory should cover every major chapter of his physiology course (which he taught single-handed in both French and Flemish, the two official languages of Belgium). Thus, in addition to the energetics of muscle contraction, the specialty of his mentor A. V. Hill, and to basal metabolism, an interest he inherited from his predecessor, the Dutch physiologist A. K. Noyons, he had groups working on the action of insulin, also started under Noyons, on kidney function, on gastric secretion, on cardiac activity, on neurobiology, and even on experimental psychology. As chance would have it, when offered the “menu,” I chose to join the insulin group. I knew nothing of the field but had been attracted to it by the lurid sight of a team performing a bloody operation, which I learned later was the removal of the liver from a dog. Thus, very unromantically, started my love affair with insulin, an adventure that was to dominate my life as a budding scientist for close to 20 years.

The Hepatic Action of Insulin—When I entered Bouckaert’s laboratory, insulin had been discovered only a dozen years before. Some of the best laboratories in the world were vying to solve the mechanism of action of the hormone. Two schools confronted each other, prolonging
a controversy that had divided the field of diabetes research for more than 50 years. On one hand were the advocates of the liver and on the other those of the “periphery,” mostly the muscles. The hepatic theory went back to Claude Bernard, the discoverer of the “glycogenic” function of the liver. Partisans of this theory attributed the characteristic hyperglycemia of diabetes to “overproduction” of glucose by the liver and believed that the main effect of insulin was to inhibit this phenomenon. The opposite theory held “underutilization” of glucose responsible for the elevated blood sugar in diabetes and viewed insulin as primarily stimulating the uptake of this sugar by the muscles.

By the time I joined the fray, as no more than a timid onlooker at first, there was general agreement on the peripheral effect, which had been convincingly demonstrated in particular by a famous team (2) that included Sir Henry Dale, who was to win the 1936 Nobel prize in medicine, Charles Best, co-discoverer of insulin with Banting but ignored by Stockholm when this discovery was recognized by the 1923 prize, and a young Belgian investigator from Louvain, Joseph P. Hoet, who had since become a distinguished diabetes specialist and was, for this reason, something of a local competitor to Bouckaert, symbolically opposing clinical to basic research. The role of the liver, however, continued to be hotly debated, with (at the time I am writing about) a distinct majority against it. Many workers, including the team just mentioned, denied any inhibition of hepatic glucose production by insulin. Some even claimed, on the strength of impressive results, that insulin actually enhanced this process, thereby helping to supply the muscles with the extra glucose they were utilizing under the influence of the hormone. Among the more committed defenders of this intellectually appealing theory were Carl and Gerty Cori in the United States, about whom I shall have more to say later.

Bouckaert’s contribution to the field was modest but pertinent. He felt that studying the effect of insulin by injecting animals with the hormone was complicated by the animals’ reaction to hypoglycemia, which included a discharge of epinephrine, a hormone known to stimulate hepatic glycogenolysis. Thus, it seemed quite possible that the observed enhancement of hepatic glucose production was not because of the injected insulin itself but due to epinephrine secreted by the adrenal glands in response to the elicited hypoglycemia. To avoid such artifacts, Bouckaert had devised a technique known as the “compensation” technique in which animals injected with insulin were given a continuous intravenous infusion of glucose adjusted, by trial and error, to keep the blood sugar level unchanged (3). Others had done the same thing, of course, but with less precision. Furthermore, in Bouckaert’s hands the amount of glucose injected, the so-called “compensation dose,” became a quantitative measure of the effect of insulin expressed in terms of glucose consumed. Indeed, except for possible fluid expansion, the amount of glucose injected to maintain a constant blood sugar level was obviously equal to the extra amount of glucose used under the influence of the hormone.

As a first application of this technique, the group had measured the compensation dose needed by rabbits injected subcutaneously with increasing amounts of insulin. A nice hyperbolic relationship was observed, indicating saturation of a receptor and plateauing at a level, called the “maximal effect” of insulin, where further increases in the amount of insulin injected no longer increased the compensation dose (3). Subsequent experiments were all performed on animals injected with a “supramaximal” dose of insulin, thereby avoiding dosage effects. Interestingly, dogs needed considerably more glucose than did rabbits to compensate for the effect of a supramaximal dose of insulin.

As a next step, Bouckaert tackled the liver problem by the simple device of measuring the compensation dose in whole animals and in hepatectomized animals. It is at this stage that I joined the group, taking charge more and more of the conduct of the experiments as older students involved in the project left the laboratory and De Nayer became increasingly preoccupied with other projects. Similar experiments were also performed on totally eviscerated animals and on animals injected with various substances (for example, epinephrine.

The most spectacular finding and the only one of interest for the present account was that hepatectomized dogs needed considerably less glucose to be kept normoglycemic after injection of a supramaximal dose of insulin than did intact, similarly anesthetized animals. The conclusion was drawn, enthusiastically if not very critically, that the liver is the major site of insulin action. Taking our results at face value, it seemed that the hormone not only inhibits hepatic glucose production but even strongly stimulates the uptake of glucose by the liver as
it does in muscle. The great controversy was finally solved. The liver was the winner, at least
in quantitative terms! Before the triumph could be savored, however, the war had broken out.

**Under German Occupation**

In this story, which is to remain strictly scientific, I shall skip my personal participation in
the conflict, which, in any case, was minimal. Let it simply be said that after some minor
adventures and a lucky escape (more comical than heroic) from a prisoners column, I found
myself back in Louvain able to complete my clinical training and to take my final examinations. I graduated as an M.D. in the spring of 1941 facing bleak immediate prospects but
looking forward to a future that I never doubted was to see the final defeat of the Nazis.

**Filling Time, Preparing for the Future**—There would be much to tell of those war years, but
I must stick to my subject. I did my best to pursue my goals despite the difficulties imposed by
the war conditions. Having realized that my ambition to elucidate the mechanism of action of
insulin on the liver could not possibly be fulfilled by the simple technologies I had used so far
but required more incisive, biochemical approaches, I decided to take advantage of my enforced
inactivity in the laboratory and to go back to school to learn chemistry of which I knew only the
bits that were taught to medical students. I was able to do this while supporting myself by
working as a clinical assistant in the cancer institute, doing mostly night duty.

Despite these demanding activities, my love affair with insulin went on unabated. Experimental work being out of the question, I decided to put our results in order and wrote them up in a series of papers that appeared between 1944 and 1946 in the *Archives Internationales de Pharmacodynamie et Thérapie*, a journal published in Ghent under the direction of Corneille Heymans, who was kind enough to accept my first efforts (4–7). In addition, I still found time for reading, wading through much of the work published until then on diabetes and insulin and organizing it in a 400-page book containing more than 1200 references. This work actually found a publisher. It appeared in 1945, simultaneously in Brussels and Paris, under the title *Glucose, Insuline et Diabète* (8). It was condensed into a dissertation containing mostly the experimental work with which I was able, in 1945, to conquer the degree of “Agrégé de l’Enseignement Supérieur,” a sort of glorified Ph.D. that served as a prerequisite for obtaining a professorial position.

I also wrote an English review covering the laboratory’s work on insulin as well as some of
my thinking on the subject. This paper was published in *Physiological Reviews* in 1947 (9)
thanks (as I remember) to the recommendation of Dale, who did not like it but felt that having
been isolated during the war we should be allowed special latitude. All this writing, I must say,
was very much a solo exercise. Bouckaert, whose name appeared as last author on the
experimental papers and as first author on the review, left me an essentially free rein. De
Nayer had left the laboratory to take over the directorship of a new sports institute, and my
fellow students had disappeared without a trace. Fortunately, links of my family with Eng-
land, where I was born during the previous war, had made me sufficiently familiar with the
English language so that I could write an acceptable text for the review. All these activities did
not prevent me from getting married in 1943 to a wonderful lady, who is still my wife today and
who gave birth to our first two children in 1944 and 1946.

A central point in my thinking at the time, obviously influenced by Bouckaert’s insistence on
keeping the blood glucose level constant but also bolstered by much of what I had read, was
that the rate of glucose utilization by the tissues, including the liver, is directly proportional
to the glucose concentration in the blood independently of any hormonal influences and due
simply to a mass action effect. I was particularly impressed, in defending this notion, by the
work of an American investigator, Samuel Soskin, who had championed the concept of a
“hepatic threshold” for glucose, defined as the blood glucose level at which glucose production
and utilization by the liver exactly balance each other (10). According to Soskin, the hepatic
threshold for glucose was elevated in diabetes and lowered by insulin. In this, he ran counter
to the opinion held by the majority of workers, in particular the Coris, who dominated the field
and (as I learned later) had made the controversy into something of a personal feud.

Blissfully unaware of these undercurrents at the time I wrote my thesis, I enthusiastically
endorsed the concept of a hepatic threshold for glucose and incorporated it into a general
theory of insulin action according to which the hormone has the same effects as hyperglycemia
and, therefore, must favor whatever process is subject to the mass action effect of glucose
concentration. Not much remains of this theory except for the fact that liver glucokinase,
contrary to other hexokinases, has a high enough $K_m$ for the rate of the reaction it catalyzes to be influenced almost linearly by concentration changes in the range of the normal blood glucose level. Theorizing apart, my reflections produced an unexpected side effect that turned out to be of some significance, not only for my career but even for the field. I rediscovered glucagon.

**Glucagon, My First (Re)Discovery**—Among the various papers that I had read dealing with the possible effects of insulin on the liver, one by Bridge (11) had given me special trouble because it flatly contradicted the theory that I strongly believed for many reasons to be correct. Yet I could find no fault with it as the author had kept his animals constantly hyperglycemic by a continuous infusion of glucose. Nevertheless, addition of insulin to the infused glucose, while furthering the synthesis of muscle glycogen, inhibited liver glycogen formation in a dosage-dependent fashion, offering what appeared as incontrovertible support for the Cori theory that insulin favors the transfer of glucose from the liver to the periphery. This work had worried me to such an extent that I had devoted some 4 pages to its description in the book I was writing.

Then, as told elsewhere (12), a thought suddenly flashed through my mind on a bright day in May 1944 as I was walking through the rubble-strewn streets of Louvain, which two nights before had been devastated by a disastrously misdirected bombing by allied planes. The thought focused on one word: glucagon! I knew of this substance as a hyperglycemic impurity that accompanied insulin through several purification steps but was removed by crystallization of the hormone according to a method devised by Abel (13, 14). After eliciting a flurry of interest in the late 1920s, glucagon had since been largely forgotten even though clear hints existed in the literature, as I found out later, that it may have made a comeback. What happened was that a simpler technique for crystallizing insulin in the presence of zinc had been worked out by Scott (15). Unbeknown to the investigators, the impurity had been reintroduced into insulin preparations.

That something of the kind may have happened was the suspicion that occurred to me on that day in May 1944 as a possible explanation of Bridge’s results. It implied that the insulin used by the American investigator, which was made by the Lilly company, must be contaminated with glucagon, whereas the brand we used, which was British (Allan-Hanbury) before the war and Danish (Novo) during the German occupation, had to be free of this contaminant because it had given no sign of a paradoxical effect on the liver. I included this proposed interpretation in my book but had to await the availability of Lilly insulin before I could test it experimentally.

I did not have long to wait. The Allied forces entered Louvain on September 4, 1944. I duly celebrated the event on September 5 and went the next day to the American headquarters, where I managed to see a doctor and to obtain from him a few vials of the precious product. The same afternoon, with a young medical student, Henri-Géry Hers, who became my first co-worker and was to share many of my later scientific adventures, I injected some of the material into one of the rabbits that, fortunately, were still raised in the physiology institute because the institute’s garden provided all the food they needed and the caretaker found them to be a profitable source of meat. I shall never forget the telltale, initial rise in blue tinge that preceded its subsequent fading in the row of test tubes containing the blood samples we had taken and had analyzed for glucose by the time-honored Folin-Benedict reaction (which relied on the reduction of cupric to cuprous ions, producing a blue color under the conditions used). Lilly insulin produced an “initial hyperglycemia,” the signature of glucagon. The Danish Novo insulin, when tested in the same manner, did not cause an initial hyperglycemia. I felt like the French astronomer Le Verrier when the planet Neptune, which he had calculated must be there, was actually discovered.

Later, at Hers’ suggestion, we used the compensation method to verify our prediction, adding increasing amounts of Lilly insulin to the glucose that was injected into animals treated with a supramaximal dose of Novo insulin. As more Lilly insulin (acting mostly through its glucagon because the animals were already saturated with insulin to start with) was added, less glucose had to be infused to keep the blood sugar level constant until a point was reached where no glucose was needed at all. A constant infusion of pure Lilly insulin entirely neutralized the combined blood sugar-lowering effects of the Novo insulin given at the start and of the true insulin present in the perfusate! Nothing of the kind happened when Novo
insulin was added to the infused glucose. On the contrary, even more glucose had to be
provided because the animals were kept continually saturated with the hormone.

Communicated for the first time in May 1945 at a meeting of the Sociétée de Biologie in
Brussels (16, 17), these results were included in the *Physiological Reviews* paper (9). They
contributed significantly to my later acceptance by experts in the field, including the Coris.
However, before coming to that stage I must briefly refer to a temporary infidelity to my
beloved insulin, not because of any new infatuation but imposed by the exigencies of my
training as a biochemist.

*A Brief, Post-war Infidelity*

For the 3 years that followed the liberation of Belgium, I had to leave insulin on the back
burner and devote myself to the biochemical training I aspired to. This required my completing
the dissertation for a master's degree in chemistry. I gained this degree in 1946 with a work
dealing with the purification of penicillin. How this came about is a story in itself but
irrelevant to the present account.

Next came actual biochemistry, which had not been part of the curriculum I had followed as
it was not recognized as a valid discipline by the science faculty at that time. One of the
professors of organic chemistry referred to it contemptuously as “kitchen chemistry,” (actually
not a bad description, historically speaking, though not in the pejorative sense in which it was
meant). I acquired my biochemical training in Sweden in the laboratory of Hugo Theorell, a
world renowned expert on hemoproteins. My 18-month stay in Theorell’s laboratory was a
valuable and memorable experience in many respects. It provided me with the basic training
I needed and ended with a modest achievement, the crystallization of human myoglobin. I will
not dwell on it further because it had nothing to do with insulin, which still remained on the
back burner until the spring of 1947, when, nearing the end of my Swedish interlude, I started
thinking of a future in which I would be reunited with the object of my passion. My dream was
to inaugurate this future with a stay in the Cori laboratory at Washington University, in St.
Louis, Missouri, in the United States.

I have already mentioned the Coris as the most forceful proponents of the theory that I
myself held to be false. I had, because of this, conceived the naive project of spending some time
in their laboratory, never doubting for one moment that I would make them see the light that
was so glaringly evident to me. I had, in the meantime, been offered and had accepted a
position as lecturer in physiological chemistry in the medical school of my Louvain alma mater,
and my new responsibilities required me to be on duty at the latest at the end of January 1948,
which meant that I could spare only a few months for my contemplated stay in the United
States.

When I wrote to Carl Cori outlining my request, his answer was coldly negative, alleging
that he never accepted anybody for less than a year and adding: “With you, there is the
additional difficulty that we do not see eye to eye with respect to the mechanism of action of
insulin.” I was shattered because our disagreement was the very reason that had motivated
my application. Then, a few weeks later came a second letter from Cori: “You may be interested
to hear that Dr. Earl Sutherland, in my laboratory, has just discovered that the glycogenolytic
effect of insulin on liver slices is due to an impurity. I believe you have also done some work
on this subject.” There followed an invitation to come over and collaborate with Sutherland.

What this letter alluded to was a paper by Shipley and Humel (18) describing the stimulation
of glycogen breakdown in rat liver slices incubated in the presence of insulin. This paper
had attracted Cori’s attention for obvious reasons, and he had asked Sutherland, who had
newly joined his laboratory after a stint in the Army, to investigate the matter. As Cori’s letter
implied, Sutherland had found that the glycogenolytic effect was not due to insulin itself; it
persisted when the hormone added (Lilly’s, of course) had been inactivated by cysteine or
alkaline treatment (19). I don’t know to what extent he was influenced by my findings in doing
this experiment, but it is clear from Cori’s letters that they were familiar with my work,
probably through the *Physiological Reviews* paper (9).

My efforts to secure from Belgian sources the support I needed for my projected trip were
unsuccessful, but the problem was finally solved with the help of Theorell, who obtained a
fellowship for me from the Rockefeller Foundation, which was supporting his laboratory. My
Belgian failure thereby turned into a blessing, because my own laboratory in Belgium was
later to benefit greatly from my early association with this powerful foundation.
I spent only four months in the Cori laboratory, from the beginning of September to the end of December 1947. I did not see much of the Coris and never had my projected discussion with them. One reason for this was that 1 month after our arrival the Coris had received news that they were jointly awarded one half of the 1947 Nobel prize in medicine (the other half went to the Argentinian Bernardo Houssay) for their “discovery of the catalytic conversion of glycogen.” I hasten to add that we met many times after that and became great personal friends.

The announcement from Stockholm created much excitement in the laboratory. Having been privileged to attend the Nobel ceremonies the year before (through Theorell, who was a member of the Nobel Committee for medicine), my wife and I became something of experts on the topic. My wife, in particular, was able to give Gerty, who paid little attention to her attire, some valuable advice concerning dresses. I myself remembered (although it had not struck me at the time) how a few months earlier Theorell had quizzed me on the Cori achievements, which were not in his personal field of expertise.

My disagreement with the famous couple with respect to the hepatic action of insulin did not, of course, blind me to their enormous merits. They were among the founders of metabolic biochemistry. In particular, their discovery of phosphorolysis, the splitting of a bond with inorganic phosphate, had been an illuminating key to the understanding of bioenergetics, showing how the energy that would normally be dissipated by hydrolysis could be conserved in the generated phosphate ester bond. This finding paved the way for the discovery of RNA phosphorylase by Marianne Grunberg-Manago and Severo Ochoa (a Cori pupil), which played a major role in the unraveling of the genetic code, and to the discovery by Arthur Kornberg (another Cori pupil) of DPN (NAD) pyrophosphorolysis, a reaction that, reversed, was to account for the biosynthesis of the coenzyme and in due course for that of DNA.

Interestingly, a Cori finding that had particularly caught the attention of the Nobel Committee was the observation that purified glycogen phosphorylase, when incubated with glucose 1-phosphate (the “Cori ester”) and a glycogen primer, catalyzed the synthesis of glycogen or, to be more precise, of an amylose-like, linear glucose polymer (branching had not yet been discovered) that gave a blue color with iodine instead of the normal mahogany tinge (the so-called “blue” glycogen). For the first time, it was hailed, a biological macromolecule had been synthesized in the test tube. What was not known at the time is that this feat was a pure artifact. Phosphorylase never synthesizes glycogen in living cells, the local concentration of inorganic phosphate being such that the phosphorolytic direction is always favored. It befell the Argentinian Luis Leloir (yet another Cori pupil) to identify the true mechanism of glycogen synthesis (from UDP-glucose). Needless to say, this historical detail in no way detracts from the monumental importance of the Cori contributions.

My memories of the Cori laboratory bring up the image of a beehive in which small individual groups worked in separate laboratories on distinct problems, which they were not encouraged to discuss with each other. Already in those days, competition weighed on personal relations and fraud was not absent. The Coris themselves were victims of fraud by one of their co-workers and had to rescind a paper. The “omerta” law was poorly observed; we were all members of a happy family and freely talked science when we met on social occasions.

Because of the pressure of time, my personal contacts were largely restricted to Earl Sutherland. He was very different from me in temperament. Outwardly jovial and easygoing, he rarely betrayed (behind a deceptively casual and self-deprecating attitude) the intensity of the passion that drove him. Only when he was opposed and convinced he was right did he become obstinately unyielding. Anything but a Cartesian, he had a keen mind but a baffling, circumlocutory way of expressing himself, often voicing only the final conclusion of some long internal monologue that was left to be guessed but, when divined, often proved strikingly pertinent. His approach to research was essentially pragmatic and intuitive, seeming to rely more on instinct and flair than on rational reasoning. Typically, when we later independently tried to elucidate the mechanism of the glycogenolytic effect of glucagon and epinephrine, he unerringly picked on phosphorylase as the target of the hormonal action, a finding that eventually led him to discover cyclic AMP. On my part, I had tried every possibility I could think of but had excluded phosphorylase a priori because the enzyme was believed (see above) to catalyze the synthesis as well as the breakdown of glycogen and I knew that “the activity of a catalyst is without influence on the equilibrium of the reaction it catalyzes.” Earl knew it too, but the knowledge did not constrain him.
Reflections: My Love Affair with Insulin

Despite our differences in personality, we made an excellent team and became close friends. We shared a burning interest in our problem, a concern for quality, and an almost untiring capacity for work, often laboring until late at night before ending for a snack in the only diner of the neighborhood that was still open, a hovel called “The Pig’s Ear.” A skillful experimenter, Earl taught me much, including his gift for cutting thin liver slices that continued to perform beautifully when incubated in vitro.

Our partnership proved fruitful. In four hectic months, we showed that glucagon is made by no other tissue than the pancreas except, surprisingly, the gastric mucosa and certain other parts of the digestive tract. Using a variety of approaches, we obtained strong evidence indicating that pancreatic glucagon was probably a hormone made in the endocrine islets by cells different from the insulin-producing beta cells, presumably the alpha cells. Incidentally, we did not call the substance “glucagon.” Earl had taken a strange dislike to this term and insisted on the cumbersome name of hyperglycemic-glycogenolytic factor or H-G factor. Several years later I decided to reinstate the old name after having read Warburg’s memoirs, in which the great German biochemist recalled an old dispute with David Keilin concerning the name of the “respiratory enzyme,” settling the matter by categorically stating that “it is the right of the discoverer to name his discovery.” It seemed to me that this right belonged to the original discoverer of glucagon, an American named J. R. Murlin, and that we had no right to change his chosen term just because we didn’t like the sound of it.

This is as far as we could go. Only after I returned to Belgium was I able to bolster the alpha cell hypothesis further by showing, in collaboration with Charles Vuylsteke, that treating guinea pigs with cobalt (which my colleague, the anatomy professor Ernest Van Campenhout, had found to selectively damage the islet alpha cells) caused a drastic lowering of the glucagon content of the pancreas. We also found that the pancreas of birds, which is particularly rich in alpha cells, has a correspondingly high content of glucagon.

Our St. Louis findings were published under the names of Sutherland and de Duve. The Coris generously refused to add their names on the paper, which they could have done but felt they had no right to do, not having participated in the work in any way. My suggestion that the credit be shared equally between Earl and myself by splitting the publication into two papers, with each of us appearing as first author on one, was adamantly turned down by Earl. It was one of the rare occasions when his inner ego was allowed to surface.

My stay in St. Louis yielded other dividends. First, it brought me in contact with the Lilly company, which, far from penalizing me for showing their product to be impure, actually took over the purification and sequencing of glucagon and, in addition, generously added me to the small, privileged network of investigators (including, prominently, the Coris) they supported financially and invited regularly to their annual “Insulin Conferences” in Indianapolis. Without this invaluable support, I would never have been able to start a successful laboratory after my return to Belgium or to establish the many early links with American investigators that greatly helped me to put our work on the map. Note that this no-strings-attached bounty even continued for a while after I had left the insulin field. The 1955 paper in which the word “lysosome” first appeared acknowledges the generous support of the Lilly Research Laboratories!

My return journey from St. Louis was also rewarding. It took me to Toronto, where I was kindly received by Charles Best; to Chicago, where I met Rachmiel Levine, a former associate of Soskin who, himself, was no longer active in the field; to Boston, where I called on Baird Hastings, a leader in the study of carbohydrate metabolism, and, especially, on Fritz Lipmann, one of my heroes, with whom I formed a lasting relationship; and, finally, to New York, where I paid my first visit to the legendary Rockefeller Institute for Medical Research to call on my famous countryman Albert Claude. He received me with great friendliness and gave me some of his reprints, which turned out to be of crucial importance in my later research. He also took time to introduce me to “a young man you may like to meet,” George Palade. Little did we suspect at that time that I would myself join Rockefeller some 15 years later; even less did we suspect that the three of us would one day be invited to Stockholm together. I owe an immense debt to that day in May 1944, when, amid the rubble of fuming ruins, inspiration whispered the word “glucagon” into my brain.

Back in Belgium

The rest of my story has been told elsewhere. Briefly summarized, it starts with the efforts made by the little team of outstanding young co-workers I had the good fortune to
assemble right from the start (Henri-Géry Hers, already mentioned, and two medical students, Jacques Berthet and Lucie Dupret, soon to become Mrs. Berthet) to characterize the hexose phosphatase shown by the Coris to account for the unique ability of the liver to form free glucose. The rationale for this work was that this enzyme might be responsible for the difficulties experienced in attempts to demonstrate an effect of insulin on isolated liver tissue and, thus, that more needed to be known about its properties and regulation.

Identified as a specific glucose 6-phosphatase, different from the unspecific acid phosphatase, the enzyme was found to be irreversibly precipitated at acid pH, a property that my acquaintance with Claude’s work allowed me to interpret as evidence that the enzyme was attached to some intracellular structure. This surmise, in turn, led to our using Claude’s technique of differential centrifugation, as modified by his pupil Walter Schneider, to identify the structure in question, which was found to accompany the fraction called “small granules” or “microsomes” by Claude (28).

Further work carried out largely by a medical student, Henri Beaufay, who had joined the group by then, showed glucose 6-phosphatase to be firmly attached to a lipoprotein structure (now identified with endoplasmic reticulum membranes) (29). Given the technologies of the day, it is doubtful that we would have progressed much further, let alone solved the problem, because even today the control of glucose 6-phosphatase activity in the liver is still poorly understood. However, serendipity knocked on our door with the complicity of an enzyme, acid phosphatase, that held not the slightest interest for us but was included in our assays because of earlier work in which it had served as background for the characterization of glucose 6-phosphatase (see above). To cut a long story short, acid phosphatase revealed itself as both particle-bound and “latent” in fresh liver preparations, losing both properties simultaneously upon aging of the preparations under mild conditions. The “hidden enzyme” proved an irresistible attraction. Insulin, my beloved, was ignominiously dropped, and all my energies were spent chasing after the elusive new particles. They turned out to be digestive bodies or “lysosomes” (26) and close by were hidden other particles, the “peroxisomes” (30). With apologies for putting further strain on an already exhausted metaphor, these two particles became my paramour and remained so for most of the years that followed. They kept me and a large number of collaborators on both sides of the Atlantic wholly engaged for the remainder of my scientific career.

The break with my former love was not brutal. That affair dragged along for a few more years, during which I tried to keep insulin and glucagon alive in the laboratory and enjoyed the satisfaction of witnessing the demonstration that the conversion of labeled glucose to hepatic glycogen, both in intact rabbits and in isolated rabbit liver slices, is enhanced, modestly but significantly, both by an increase in glucose concentration and by adequately compensated insulin, while being inhibited by glucagon (31). Two lectures, my insulin swan songs, landmark that period for me. In 1952, I was invited to give the Banting Memorial Lecture of the British Diabetic Association at the First Congress of the International Diabetes Federation in Leiden. I spoke on glucagon (21). In 1956, I attended a meeting at the CIBA Foundation in London, where I last met Gerty Cori a few months before her indomitable spirit finally succumbed to the fatal disease that first declared itself at the very time of my stay in St. Louis, as recalled in this journal by Kornberg (32). I spoke on the hepatic action of insulin, receiving a sympathetic reception from Gerty and Carl, both of whom I recall with deep emotion (33).

Fortunately for the field, Hers did not, unlike my other co-workers, follow me in my new research direction. He remained faithful to carbohydrate metabolism to which he contributed a number of valuable findings, starting with the elucidation of the pathway of fructose metabolism, the “Hers pathway,” which he found to involve the aldolase-mediated splitting of fructose 1-phosphate rather than the conversion of this ester to fructose 6-phosphate by a mutase, as postulated by the Coris, once more crossing paths with the famous pair. Later, he made many detailed contributions to our understanding of glycogen metabolism and its control culminating in his discovery (with Emile Van Schaftingen and Louis Hue, who brilliantly follow in his footsteps today) of fructose 2,6-bisphosphate (34). Who would have thought that a hexose phosphate ester was still waiting to be discovered 50 years after the isolation of glucose 1-phosphate by the Coris?

In his work on glycogen, Hers had become interested in the congenital anomalies of glycogen metabolism, and in particular the glycogen storage diseases, which had been Gerty Cori’s last
research interest. After her death, he pursued her work and undertook a systematic search for the missing enzyme, using pathological specimens of these rare conditions collected from various clinical centers. This is how he ran into the mysterious type II glycogenosis (Pompe’s disease) in which all the known enzymes of glycogen breakdown showed normal levels and the patients even responded normally to glucagon and epinephrine. However, the liver, muscles, and heart of these patients showed grossly elevated glycogen contents, leading to the death of the victims at an early age. Eventually Hers succeeded in identifying the deficient enzyme, which turned out to be an α-glucosidase with an acid pH optimum, not previously known to have anything to do with glycogen metabolism.

In another laboratory such a finding might long have remained unexplained. In ours, an acid hydrolase immediately called to mind lysosomes. The technology was available, and the enzyme was rapidly identified as, indeed, belonging to lysosomes. On the strength of this discovery, Hers proposed his concept of inborn lysosomal disease (35), an enormously fruitful notion that turned out to apply successfully to most polysaccharidoses, lipidoses, and other storage diseases (36). Thus was elucidated, with important consequences for diagnosis, prevention, and therapy, a vast chapter of pathology that had remained totally mysterious until then, and thus had the unpredictable fortuities of research brought Hers and myself back together years after our paths had diverged.

**The Moral of the Story**

It may seem inappropriate to use the term “moral” in connection with a love affair that ended in betrayal, but I should like to formulate three recommendations derived from the experience.

First, choose your mentors well. The art of scientific research is not learned in books. It is, like the crafts in the Middle Ages, learned at the bench under the direction of a master. It has been my good fortune to work under and with a number of such masters, each of whom has taught the importance of technical excellence, rigorous reasoning, and intellectual honesty.

I should add, for the benefit of those who are becoming mentors themselves, that it is equally important to choose one’s co-workers well. I have been blessed with a number of outstanding collaborators without whom I would never have accomplished the work that is credited to me.

Second, keep your eyes open for the odd or unexpected and never dismiss it simply because it does not fit within your program. If chance offers you a clue, follow the trail. You may not discover what you were looking for, but what you discover may be more interesting than what you were looking for. In retrospect, I find that my greatest luck came from the unforeseen: insulin that wasn’t and mitochondria that weren’t.

My last recommendation is for the powers that be. Fund the investigator, not the investigation. Do please remember, I beseech you, this self-evident yet rarely recognized truth that science, at least its spearhead called basic research, explores the unknown and is therefore unable, by definition, to predict how useful or profitable its discoveries will be. Rather than demanding assurances on this account that cannot possibly be honestly provided, put your trust in the investigator’s skill, instinct, curiosity, and motivation. This will produce the best research contributing best to the advancement of knowledge, the true aim of science. Whether useful or profitable applications arise from new knowledge will be revealed only after the fact.

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