Guillemin and Schally: A Race Spurred by Rivalry

The rivalry between Roger Guillemin and Andrew Schally in pursuit of the brain's hormones spans a period of at least 21 years. The marathon started in 1955, when each discovered that the interaction between brain and pituitary gland can be demonstrated in tissue culture. The isolation of thyrotropin releasing factor, TRF, in 1969 marked the first lap of the race; identification of luteinizing hormone releasing factor, LRF, 2 years later was the second milestone, and the third was the isolation of GIF or somatostatin, achieved by Guillemin's team in 1973 and by Schally's in 1976. Last year, the two arrived neck and neck at the finishing post which Alfred Nobel set up for aspiring scientists in Stockholm.

This is the third of three articles about the pursuit of the brain's hormones by Roger Guillemin and Andrew Schally.

Conventional opinion has it that the TRF lap was substantially a draw, that Schally forged ahead down the LRF straight, and that Guillemin caught up on him with somatostatin. But the matter of who won is, past a certain point, an unilluminating question: the race was an interaction. The interesting questions are those that shed light on the nature of their joint achievement. Why did Guillemin and Schally succeed when others failed? How did their rivalry differ from the usual forms of scientific competition? Did it hasten or impede their progress?

How to Win a Nobel: Shun Distractions

One of the salient features of Guillemin's and Schally's approach has been their refusal to be diverted by other problems. Each made isolation of the factors his paramount goal. The elegant physiological experiments were done by others. Geoffrey Harris established the theory of hypothalamic releasing factors. Harris and S. M. McCann demonstrated the existence of LRF. McCann pointed the way to somatostatin. They, no less than Guillemin and Schally, realized the importance of isolating the postulated factors, and set up programs to do so.

Neither Harris nor McCann lacked the physiological skills to track down the factors. But neither was willing to lay aside the other problems in the field and concentrate his full energy and resources on the isolation program. One reason may have been the lack of theoretical interest in isolation procedures: "Most intelligent people won't do isolation work—I think my IQ went down about 20 points while I was doing it," jokes Cyril Bowers, the Tulane University endocrinologist who helped Schally solve the structure of TRF.

The isolation programs do demand considerable intellectual discipline and frugality. A constant temptation is to divert portions of the critically small amount of isolated material to experimental use, both for interest and because publication of the work gives something to show. "It is not much of a life for a physiologist," Guillemin reflects: "For years I refused to do elegant physiological work on TRF because I knew that whatever I took for physiological studies would be subtracted from the world supply available for determining the structure. That was a major reason why neither Harris nor McCann reached the structure—98 percent of their stuff went for physiological studies."

Work Humbly with Your Chemist

A key to success, Guillemin believes, is that the physiologist "must work humbly with the chemist," particularly in providing quick answers on whether a fraction is biologically active, so that the chemist can proceed with the next step. This means using a speedy assay, even if it is of doubtful physiological relevance. Harris, Guillemin suggests, was not intellectually ready to accept this practical proposition: "I knew Harris could never isolate LRF because he had chosen the wrong assay. With his method, infusing a fraction into the pituitary of a rabbit and watching for ovulation, it took 4 months to get an answer. The time and cost were such that his chemist lost interest."

Harris's able chemist, Peter Fawcett, went to work with McCann. McCann faced the hard decision of whether to abandon his physiological studies and sink everything into an isolation program. The difficulty of the choice is still besetting. To operate on the Guillemin-Schally scale, McCann says, "I would have had to put all my money into buying hypothalami. I was reluctant to do that, because it would have meant jettisoning everything. Looking back on it, maybe we should have."

Rather than an all-or-nothing gamble, McCann took the eminently sensible course of mounting a medium-scale isolation program in parallel with his physiological research. His team was ahead up until 1969, he believes, when the other two solved the structure of TRF. After being beaten on LRF in 1971—even though the McCann team had come close to solving the first three amino acids of the structure a year before—a certain depression set in and "we couldn't generate the enthusiasm to really push on GIF [somatostatin]. But we probably wouldn't have gotten it because our assay system was not as sensitive," McCann reflects.

Interesting experiments can be one distraction; another is the fascination of developing new techniques, which can easily become an end in itself. "One surprise is that these two groups developed very few of the methods they used," observes Murray Saffran, Schally's teacher and a long-time participant in the field. Both groups agree that they adapted existing techniques to their purposes rather than developing new methods themselves. "I spent many years devising better systems before I realized that fiddling with methods had very few rewards. I decided our aim was isolating the structure," says Schally. "We have not developed any revolutionary new techniques, although we were the first to apply certain techniques to our field," comments Roger Burgus, the Guillemin team chemist.

Bold Jump for Academics

The singlemindedness of the two teams extended to matters of organization. Guillemin and Schally each realized that it was essential to build up a strong team with members competent in the various disciplines involved. Each also understood that hypothalamic material had to be collected and processed on a semi-industrial scale. Neither operation is within the customary experience of an academic biologist. "I think what Guillemin did that others didn't was that he organized to get more material," comments Burgus; "I expect that Fawcett [McCann's chemist], given the same sort of budget and backing, would have come up with the same sort of

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structure." Wylie Vale, the Guillemin team physiologist, has a similar analysis: "What was tough was having the courage to set about organizing the collection of a million sheep brains. It was also tough to say 'I am going to put up with decreased productivity during the time I devote to a long-term project of uncertain outcome.' That is some jump for an academic scientist." McCann, who chose to remain an academic scientist (neither Guillemin nor Schally is at an academic institution) was unable to follow up his discovery of somatostatin, in Vale's view, "because although he had an excellent team, it was never as dedicated to the single issue of isolation as were Guillemin's and Schally's."

The Stimulus of Rivalry

Dedication was a salient ingredient in each team's success. Another ingredient, though harder to quantify, was the intense competition between Guillemin and Schally. Most observers, while differing in their emphasis, agree that the rivalry was a factor in the two teams' progress. Joseph Meites, a neuroendocrinologist and unofficial historian of the field, believes that "although their rivalry certainly served as a stimulus, they would have succeeded without it." Wylie Vale sees the rivalry as a strong motivating force: "I think the competition was a positive factor on balance—it produced a lot of motivation and led to greater efforts and more focusing of those efforts."

The rivalry no doubt stemmed in large part from historical circumstances. Through making the same important observation at an early stage in their scientific careers, the two established independent and equal claims on the same problem. But the rivalry must also have been shaped by their respective characters. "Both are very ambitious, hard working individuals who were absolutely determined to do all they possibly could," remarks Joseph Meites. "We worked very hard, because that is in the marrow of both us," Guillemin says of the years at Houston with Schally. The industry was allied with a strong vein of competitiveness. According to one observer, "Both of them have a strong tendency to look on things in terms of us versus them." Several acquaintances of each insist that the overt differences in character are only skin deep. "They are unusual types of individuals, to say the least," remarks Schally's colleague Abba Kastin; "At first impression you think they are just two entirely different people. You see Guillemin as sophisticated, urbane, and charming, Andrew as very candid, caring little for the social amenities. Neither impression is inaccurate, yet underneath they are in many ways identical."

Hysterical Competition

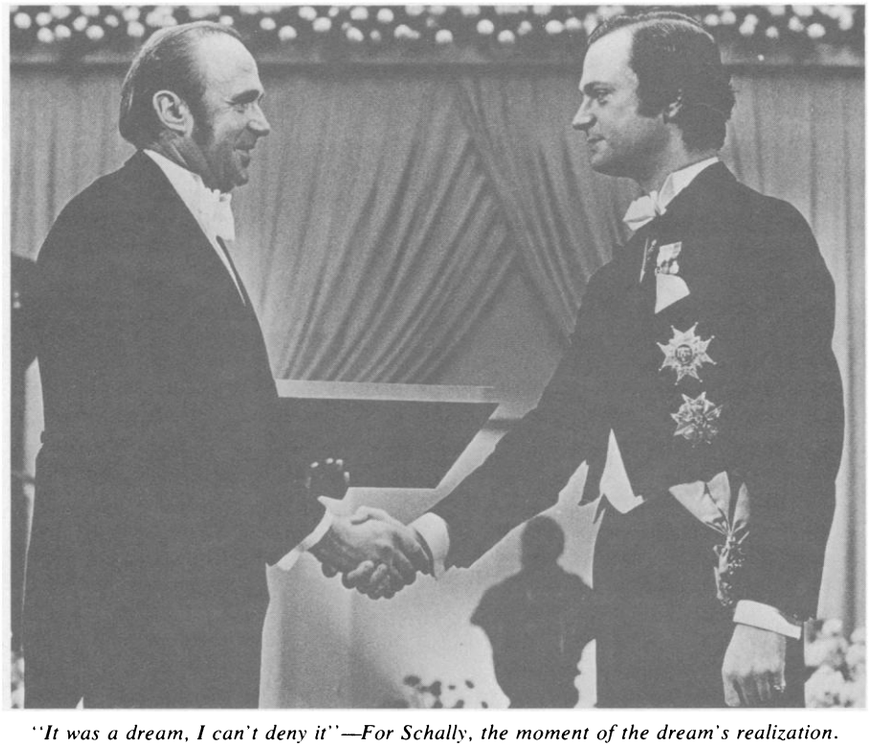
The Guillemin-Schally rivalry seems to have differed from ordinary scientific interactions in the extent of its personal focus. It is important to note Guillemin's belief that the relationship with Schally was in fact no different from the ordinary forms of scientific competition and can not even be called a race. Other observers have generally different views. "They were bitter rivals, to put it mildly," says Meites: "It was well known among endocrinologists and could be observed right out in the open at public meetings. Essentially it was a fight as to who was going to get there first." Schally makes no bones about describing the interaction as a "race," consisting of "many years of vicious attacks and bitter retaliation." Guillemin responds that he doesn't know what Schally is referring to or what "microepisodes" he has in mind.

Walter Hearn, Schally's predecessor as Guillemin's chemist from 1954 to 1955, believes "it is fair to say that right at the beginning, from their very first publications [in 1955], there was this competition." The rivalry at that stage concerned the different name and method of assay used by each for CRF. Schally joined Guillemin's laboratory in 1957 (both Schally's—or rather, Saffran's—assay method and name for CRF prevailed) and the two worked together cooperatively, even if not always without tension. "It was only after Schally left Houston, when he was head of his own group, that some of these unpleasant exchanges started to take place," says Guillemin. "In a way he is right because we could not be vicious in the same lab," comments Schally: "But after I left him the competition became almost hysterical."

The rivalry was manifested both at scientific conferences—"At public meetings Guillemin and Schally were often at each other's throats," recalls one participant—and in articles in the scientific literature. In a recent historical review of his own work on LRF, for example, Guillemin mocks Schally's falling into the "booby trap" of thinking a fragment of pig hemoglobin was GRF, and gives his opinion that "the most important paper in the discovery of LRF by anyone was that describing the isolation of thyrotropin releasing factor (TRF)"—all within the first paragraph of the review. Schally, in a companion article on his discovery of LRF, thinks it worthwhile to deplore a wrong suggestion about TRF made by Guillemin over a decade ago.

"If He Wanted a Cold War . . ."

Sniping at each other's errors or wrong proposals has been one feature of the Guillemin-Schally rivalry. Another, in Schally's view, has been the practice



"It was a dream, I can't deny it"—For Schally, the moment of the dream's realization.

of citing as little as possible of each other's work. When Schally first started his own laboratory, "I acknowledged everything he did in my reviews in a very proper way. But in his reviews there was no mention at all of what I did. So if he wanted to have this cold war, I gave him a sample of his own medicine." Guillemin says that he has always tried to quote Schally's work fairly, and that the notion of a cold war is ridiculous.

Cold war or not, Guillemin's and Schally's differences are of less importance in themselves than as manifestations of a rivalry which both to some extent motivated their efforts and to some extent shaped them. Schally, for example, chose to work with pigs because Guillemin's isolation program depended on sheep material; Schally at first strengthened his team in physiology rather than chemistry because of "my inferiority complex with respect to Guillemin that my physiology would not be good enough." Another way in which the rivalry may have influenced progress is in the matter of exchanging materials. The scientific tradition of free exchange does not seem invariably to have been honored. Guillemin has complained that Schally refused to share his samples of synthetic TRF-type tripeptides on the grounds that " 'the FDA did not allow such transfers across state lines.' " Schally recalls refusing a request (he believes some other material was concerned) but says he did so because Guillemin would only have used it to announce that in his laboratory the material was useless: "It is like giving someone a gun so he can shoot you. What did he make so much fuss for? He was an opponent and an enemy at that time. Also I simply didn't have enough material for my own use." Schally's colleague Abba Kastin, who believes the incident concerned the factor known as MIF, confirms that he and Schally didn't have enough even for their own use.

The Effects of Competition

Whatever the particulars of the episode, it underlines the active lack of cooperation between the two teams. There

Briefing

Senate Staff Study Warns of Corporate Interlocks

According to a staff study just released by a Senate subcommittee, many of the nation's largest corporations, including the big energy companies, tend to be linked by a disturbing web of direct or indirect interlocking directorates.

The study, prepared by the staff of the Subcommittee on Reports, Accounting, and Management formerly chaired by the late Senator Lee Metcalf of Montana (who died in January), says for example that the three largest energy companies—Exxon, Mobil, and Texaco—are "indirectly interlocked" with a number of their major competitors. Two directors of Exxon, the largest company of all, serve as directors of Citicorp, one of the nation's biggest banking firms; along with them on the Citicorp board are directors of Mobil and Standard Oil of California, plus directors of a number of other energy-related companies, such as Halliburton (Brown & Root), Texas Eastern Transmission, Stone and Webster, General Electric, and Westinghouse.

The staff study does not allege that such indirect linkages are illegal under the antitrust laws, nor does it cite any specific instances of abuses. But it does argue that interlocks of this kind can represent a "danger of a business elite, an ingrown group, impervious to outside forces, intolerant of dissent, and protective of the status quo, charting the direction of production and investment. . . ."

The study recommends that Congress "enact a general prohibition against any officer or director of a company with over $1 billion in assets or sales from being an officer or director of any other company of similar size." "This may sound like a harsh proposal," the study acknowledges. "Indeed it is, because its purpose is to effect dynamic changes in the composition of major company boards. Its objective is to separate the larger corporate managements in order to encourage more innovative and competitive corporate policies and to avoid possible conflicts of interest."

Small High-Technology Firms Come Under Foreign Control

Senator Gaylord Nelson (D–Wis.), chairman of the Senate Select Committee on Small Business, is afraid that the United States may be "losing the cream of its new technology" because small, high-technology companies are finding it difficult to raise venture capital domestically. Research done by the Select Committee last year turned up evidence that control or near-control of at least 11 companies of this kind had passed to foreign investors.

For instance, a Japanese firm, Fijitsu, had acquired a 36 percent interest in the Amdahl Company of California, characterized by the committee as a designer and manufacturer of "large-scale computers more powerful than the top of the IBM line." Also, a West German company, Siemens AG, had become the largest shareholder in two other California firms, Advanced Micro Devices (a designer and producer of advanced integrated circuits) and Litronix (a manufacturer of advanced semiconductors).

Senator Nelson's concern at such acquisitions was set forth last fall in a meeting with President Carter at the White House and was repeated recently in the annual report of the Select Committee. The foreign buyers, he said, will be able "to take these new products and their technology and exploit them abroad for the benefit of foreign jobs, foreign profits, foreign exports, and foreign economic and military strength."

In its continuing series of hearings on the problems that small companies of all kinds are experiencing in raising venture capital, the Select Committee recently learned that a survey conducted by the American Electronics Association had produced some disturbing results. It indicated that, during the period 1971–1974, new electronics companies succeeded in raising only half as much start-up capital as similar companies had been able to raise during the period 1961–1964.

The Select Committee, which may issue a special report later this year on the capital-formation problem of small business, has not yet put its finger on all of the reasons why this problem exists. But one major reason is believed to be that, in their investment policies, pension fund trustees are tending to exercise excessive caution—induced partly by federal law—by not putting money in even highly promising ventures if they are still new and unproved.

Luther J. Carter

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was little communication between the two and little sharing of data. The policy seems to have reflected the attitude of the team leaders rather than the other members. "I would have preferred a more open relationship, in which we could have got on the telephone, shared data and saved each other time," says one junior team member. Another junior member describes the relationship as follows: "There is no question that we are competitors but all of the younger people in each group are interested in getting the science done without acrimony, and there have been very few negative aspects between them. It may be that all of us are trying to get along because we don't want to fall into the trap that Guillemin and Schally have fallen into. It has been personally very disturbing to be a part of those aspects."

Would progress have been faster if the two teams had collaborated instead of fighting each other? Some observers believe that the particular style of the race made no difference to its rate of progress, others that it impeded advance. Meites's opinion is that the rivalry was beneficial: "From the point of view of science, their rivalry served a good purpose. It stimulated both men to do their very best and to check each other's work. They learned from each other and it advanced the field."

But Saffran believes progress would have been faster if they had collaborated: "Instead of cooperating, they set up rival organizations and did very little to help each other in difficulties. Perhaps a little more interchange might have helped a great deal."

Kastin points out that neither group could afford to hold back any critical information for fear that the other would discover and publish it first. But the pressure to publish can also be counterproductive. In Hearn's view, "It could be argued that the intense competition kept everyone honest and moved the research along more rapidly than it would have progressed otherwise. I'm not so sure. I think the intensity of the fear of being scooped forced many investigators into publishing too rapidly, before they bothered to check everything out."

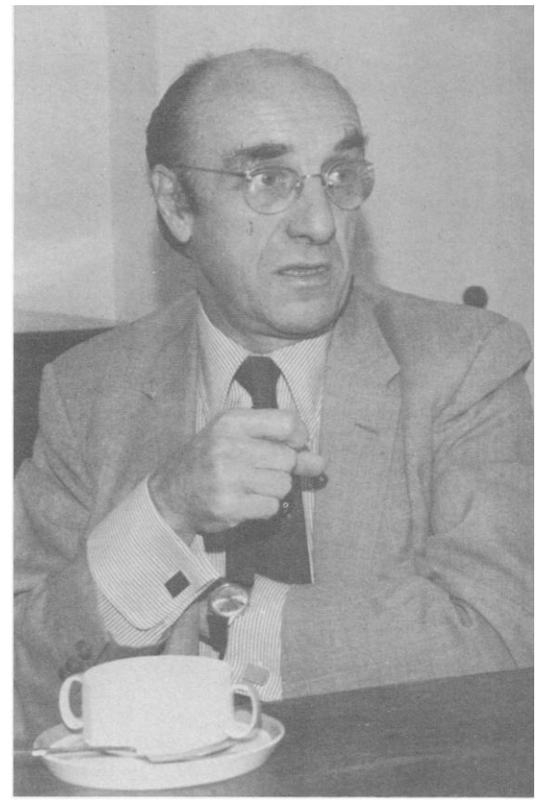
In their different ways the two principals give essentially similar responses to the question. "No two laboratories working in the same field have ever collaborated," says Schally: "Did Pauling collaborate with Watson and Crick? You just simply don't collaborate. It's a race."

As for Guillemin, "Whether it was salutary and beneficial to the field as a whole to have had two labs working on the same problem, I would say probably yes: a rich country could afford to do that."

The Lure of the Nobel

In the end what counts is success. Guillemin and Schally eventually isolated the factors they had sought for so long. The attainment of the quest, which laid the basis for what has become perhaps the most important branch of endocrinology, duly attracted the award of the Nobel prize. Was hope of winning the prize a sustaining factor in their long endeavor? "Obviously both Guillemin and Schally had strong egos that kept them going after a lot of other people had given up, including myself," notes Hearn. "Maybe they both had the Nobel prize in mind, but I never heard anything about it except in jest. After all, as a graduate student even I had asked a person who spoke Swedish to teach me how to say 'Thank you very much,' just in case." "Oh, I think it was there from the very beginning," remarks Saffran of the possibility of the Nobel prize. "I very well remember that we thought it would be important enough to be recognized," he says of the crucial experiment on CRF which he planned and published with Schally in 1955. "Despite what either may say about not caring about the prize, they've been after it for years," is the opinion of one team member, who adds his observation that "Both of them would be happier people if the prize didn't exist. It has its negative features and the world might be better off without it."

Only Guillemin and Schally know their own feelings toward the prize, and they say as follows. Guillemin avers that he never expected the Nobel prize: "I am still pleasantly puzzled to this day. I always wondered whether the discoveries involved were really worth the Nobel prize. It has been a long road, an arduous road. It required constancy, consistency and increasing know-how, but really there was nothing conceptually revolutionary in this field which made me think a Nobel prize had to be awarded for it." "It was a dream, I can't deny it," says Schally. "I worked with brilliant people in England [as a research assistant at the National Institute of Medical Research, before emigrating to Canada] and six of them got the Nobel prize. I always dreamed of it, but I was not obsessed by it." Schally knew the prize was on the cards after he discovered the structure of LRF in 1971, and has had to resist a tendency to become tense every October, when the prizes are announced. "Some people compete for 20 years and never get it. I was lucky. The committee could have waited 10 more years until I had solved CRF, PIF and MIF," he says with a flourish. "They have usually waited 11 years after the discovery being honored. But I only waited 6."



"Pleasantly surprised"—Guillemin's reaction at a press conference last year after learning he had won the Nobel prize.

For both Guillemin and Schally, the French physician and the Polish war refugee, the road that began in Montreal in the early 1950's ended in Stockholm more than two decades later. The road was long, but strikingly direct. They had chosen a problem they knew was important, and they gave it everything. Many others, some perhaps more brilliant academic physiologists than they, tried their hand and failed. Only Guillemin and Schally understood the nature of the effort that was required. For CRF, the first factor, they searched 7 years before admitting failure. Working apart, each perhaps driven by the notion that the other might claim victory first, the two embarked on another 7-year search which only in its final months was saved from summary suspension. There was no possible guarantee that the methods of the day would suffice to redeem their gamble with nature, and in the event they only barely did. Guillemin and Schally became the first to decipher the language in which the brain says to the body "Keep warm," "Reproduce," "Grow no more." For their singlemindedness and persistence, a fitting reward.

—NICHOLAS WADE