Guillemin and Schally: The Years in the Wilderness

James Watson's account of discovering the structure of DNA first brought to public attention the fact that science is a human, and sometimes highly competitive, activity. Another scientific race, compared by many who observed it with that described in *The Double Helix*, reached its finishing post last year when the two leading contenders received equal shares of the Nobel prize.

"There have been many years of vicious attacks and bitter retaliation," is how Andrew Schally describes his race with Roger Guillemin. The race has several notable features which qualify it for mention in the history of 20th-century science, and perhaps even for a footnote in the annals of human endeavor. For one thing, it lasted for 21 years, involved the creation of two rival teams of experts, and required investing time, money, and reputation in a venture which, for the first 14 years, seemed to many to be doomed to failure. For another, the enterprise, once the gamble paid off, laid the foundations for the newest and perhaps ultimately most important branch of endocrinology—study of the hormones produced by the brain itself. That the brain, the seat of intellect, should secrete hormones like a common gland is still a bizarre concept. Guillemin and Schally's isolation of the hormones is a feat which may open new doors toward the understanding of the mind, as well as to such medical benefits as new contraceptives and the control of diabetes.

The quest for the brain's elusive hormones demanded fortitude and singlemindedness. It required placing trust in techniques that were only doubtfully adequate for the job. It exposed the questers to the skepticism and mockery of their colleagues, and eventually to the threat of withdrawal of government funding. The nature of the quest was determined not just by its ends and means but also by the nature of the questers, in particular the relationship between Guillemin and Schally.

Starting Post at Montreal

"Schally is a Slav in many ways, very excitable, Guillemin is an urbane Frenchman," remarks Murray Saffran, who was Schally's thesis adviser at McGill University, Montreal. But several acquaintances of each pay little heed to the outward differences: "Guillemin and Schally have very similar personalities," remarks Cyril Bowers, a former collaborator of Schally's. In their careers there has been a striking parallelism. Both Guillemin, born in Dijon, France, in 1924, and Schally, born in Wilno, Poland, in 1926, found themselves in the early 1950's in Montreal, where each had come to study for his doctorate.

> *This is the first of three articles describing the history of the pursuit of the brain's hormones by Roger Guillemin and Andrew Schally.*

At the University of Montreal Guillemin, naturally, was in the French half of the city; Schally, whose parents had fled from Poland before the war and settled afterward in Edinburgh, was in the English-speaking half. The two did not meet in Montreal—Guillemin left for Houston the year after Schally arrived—but each acquired an interest in one of the major physiological problems of the time, the control of the pituitary gland.

At a conference many years later, at which Guillemin and Schally were having one of their then frequent confrontations, the chairman of the session, Murray Saffran, sought to break the tension by reciting a verse he had just composed:

Up in my head,
Just over my tongue,
A little thing from my brain is hung.
To make it work there are factors new
That tell it when and how much to pitu.

Everyone knew what the pituitary "pitued"; the question was how it did it. From its position in roughly the center of the head, the walnut-sized gland produces a family of hormones which themselves control the operation of other glands and tissues in the body. The pituitary directs the operation of the thyroid gland by secreting a hormone known as TSH (thyroid-stimulating hormone); it controls the reproductive cycle by a pair of hormones known as LH and FSH (luteinizing and follicle-stimulating hormones), and it shapes the body's growth pattern by secreting growth hormone. But how is the pituitary itself controlled?

Suspended by a short stalk from the floor of the brain, the gland sits in a little pocket of bone known to anatomists as the Turkish saddle. A system of small blood vessels dips into the cell and carries away the pituitary's hormonal output for distribution in the general circulation. Although so close to the brain, the pituitary does not seem to be under nervous control, because its nerve supply can be cut without any major effect. It was an English scientist, Geoffrey Harris, who first seriously urged the idea that the brain must control the pituitary gland, if not by nervous signals, then by chemical means. Right above the pituitary is the hypothalamus, a region that seems to be the emotional center of the brain. Harris supposed that the cells of the hypothalamus might synthesize pituitary-controlling hormones and release them into nearby blood vessels, which happen to be those en route to the Turkish saddle.

Harris showed that cutting of the portal vessels, as they are called, impedes the pituitary gland's production. But the idea that cells of the brain, the organ of thought, might also produce hormones was too radical to win general acceptance. Among Harris's most outspoken critics was Solly Zuckerman, an anatomist who doubled as science adviser to British prime ministers. Zuckerman announced that he had repeated Harris's experiments with the opposite results. Harris fortunately discovered that in ferrets, the animals used by Zuckerman, the portal vessels tend to grow back after being cut, which would explain why they had recovered their pituitary function.

Yet however interesting Harris's theory might be, it was clear he would make believers out of his fellow physiologists only when he had positive proof of his hypothetical hypothalamic hormones. For the rest of his life Harris tried to isolate the hormones. He failed, yet everyone seems to agree that for his part in invoking the hormones' existence he would have shared the Nobel prize with Guillemin and Schally but for his death in 1971.

A Simultaneous Discovery

Discoveries, so it is said, are made when the time is ripe for them, which may in part explain why the same discovery was made at about the same time by Guillemin, working at the Baylor College of Medicine in Houston, and by Saffran and Schally at McGill University in Montreal. Both found that pituitary

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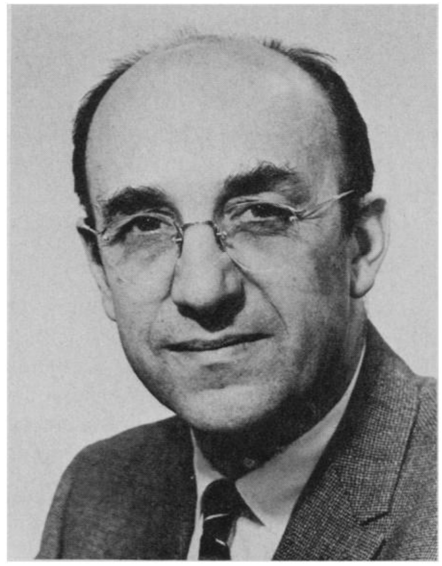
tissue cultured in a test tube will produce the usual hormones if and only if material from the hypothalamus is cultured along with it. The result both provided a compelling corroboration of Harris's theory and offered a simple test-tube system as the basis for isolating the hypothalamic hormones. Guillemin clearly recalls the day on which he observed the results of this experiment: "I still remember going home . . . [and] telling my young wife, 'I have made an observation today of such importance that you will never have to worry about our future in academic medicine.' "

The career-making discovery was followed by an almost career-destroying choice. Of all the hormones produced by the pituitary, both Guillemin and the Saffran-Schally team chose to focus on one known as corticotropin or ACTH. The hormone energizes the adrenal glands into producing other hormones which prepare the body for sudden action. Being involved in stress, ACTH was of great medical interest, and there was also an assay available for measuring it. So it was only natural to concentrate on the ACTH system and therefore to look for the particular hypothalamic factor which presumptively caused the pituitary to release ACTH.

The ACTH-releasing factor, known as CRF (for corticotropin-releasing factor), was to be the principal target of both Guillemin's and Schally's attentions from 1954 until the early 1960's. The pursuit of CRF was a hard school to learn in, for to this day it has not been found, and may not even exist as such.

The search for CRF was to create the methods that would later catch other, less evanescent releasing factors. Guillemin, whose Ph.D. was in physiology, realized that he needed the help of a biochemist. His first, Walter Hearn, joined him in 1954. One of their first problems was to obtain enough hypothalamic tissue for chemical analysis. Hearn remembers visiting a Houston packing house with Guillemin to pull some beef brains off the line. The prevailing method of slaughter was for a man to straddle the holding pen above the animal and shoot it in the head with a .22 rifle. "Roger marveled at the great accuracy with which that cowboy could hit the tiny hypothalamus so often, without even knowing what he was shooting at," Hearn recalls. The smashed hypothalami were useless. Visiting an abattoir on the same day as a rabbi, who killed the animals by cutting their throats, provided more suitable specimens.

Hearn moved to Iowa State College at the end of 1955 and continued the search for CRF for several years. He assigned the problem to one of his students, Gino Lazzari. Lazzari, however, decided CRF didn't exist: having battled many recalcitrant windmills, he declared in his 1961 Ph.D. thesis, "we yelled 'enow' and laid down our broken lance and battered hides and wrote this chronicle in warning to others who pass this way."



Roger Guillemin

Ridicule and Sarcasm in Houston

Hearn, now a writer in Berkeley, enjoyed being Guillemin's biochemist, perhaps in part because their roles were clearly delineated: "I acknowledged him as the great master and was happy that we were doing good work," says Hearn. A far less simple relationship was enjoyed by Hearn's successor, who was Andrew Schally.

Since both Schally and Guillemin had published the same basic discovery in 1955, each had an equal claim on the CRF problem. But their collaboration started on an uneven footing in that it was Schally who applied to come to work in Guillemin's laboratory, which he joined in 1957.

What made an inherently tension-laden situation yet more fraught was the attitude of other scientists. As the years passed without the capture of CRF seeming any nearer, skepticism grew in measure. "People at the time could not understand why we could not characterize CRF; the answer is that 20 years later it still hasn't been done," remarks Guillemin. "We were exposed to sarcasm, skepticism, and even ridicule and contempt by many scientists and physicians in the endocrine field who seemed not to understand the technological problems involved and the effort," Schally has written.

In such circumstances it might be expected that two strong personalities would come to blows. In fact, despite all the frustrations, Guillemin and Schally worked together for 5 years. Though CRF eluded them, they worked out the methods that would lead them to succeed where others would fail. First, they realized the scale of operation necessary to isolate the brain's hormones. It was useless to work with 50 hypothalami; the job required collecting hundreds of thousands of them and turning one's laboratory into a small factory for processing the material. Second, it was necessary to build up a strong team of experts, including particularly a chemist who knew how to fractionate the brain extract into its various components, and a physiologist who could determine by an appropriate assay which fraction held the hormone being sought. An isolation program, in other words, demanded almost total commitment of the laboratory's time and resources. This was an investment which even Guillemin's and Schally's most serious competitors, such as Geoffrey Harris in England and S. M. McCann, now at the University of Texas in Dallas, were reluctant to make.

Guillemin in 1960 took up an appointment at the Collège de France in Paris, expecting to stay permanently. Slaughterhouse procedure in Paris made easy the collection of large numbers of sheep hypothalami, which from then on became Guillemin's species of choice. But the situation at the Collège de France did not work out, and in 1963 Guillemin returned to Houston, where he had kept his laboratory open. Schally, however, was no longer there. The Veterans Administration had offered to set him up as chief of his own laboratory. In 1962 he moved to the VA hospital in New Orleans and went into business on his own.

"A Bitter, Unpleasant Relationship"

Guillemin and Schally recall the years of their collaboration from different perspectives. "In the 5 years we worked together," says Guillemin, "we never had an unpleasant word, never. We were both working hard because we were young. But I began to be disturbed by the fact that we had been working so hard for 5 years and still had not isolated CRF. Both Schally and I were becoming disenchanted with our work on CRF, and when he was offered the chance of running his own lab in the VA hospital, he accepted the position with my full blessing.

"One thing which is certain is that when Schally decided to take the VA job—which he and I had discussed, and very pleasantly so—he was totally committed to the concept that what he would do in New Orleans would be to set up a group absolutely identical to what I had done in Houston.

"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."

Schally has a different view. He describes the time at Houston as a "very bitter, unpleasant relationship. I could not stand him, he could not stand me." The crux of the problem was that Guillemin, in Schally's view, did not give him fair credit for his work. The papers of that period have Guillemin's and Schally's name first in alternate succession. Yes, "but often he would put his name on when I did the work," Schally says: "An equal partner I could be with him, but he wanted me to be his slave."

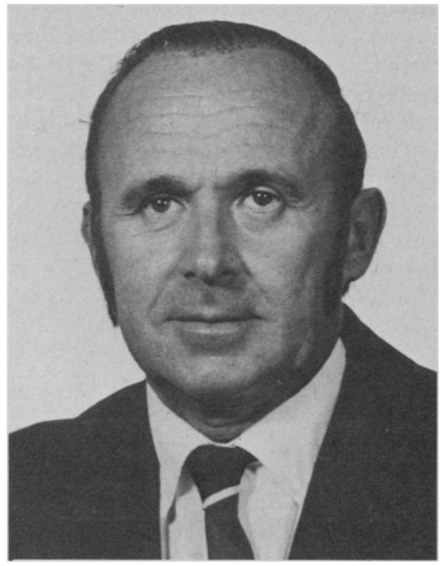
Schally's view of the relationship is significant because it influenced his scientific strategy in various ways. In building his own team at New Orleans for example, he hired physiologists rather than chemists because, he remarks, "I had an inferiority complex with respect to Guillemin as to whether my physiology would be good enough; in fact, I should have put more of my money into chemistry."

Why Schally Chose Pigs

The competition with Guillemin also dictated the species Schally chose to work with. Guillemin fixed on sheep because the hypothalamus can be removed quite easily from the skull. Pigs, the other suitable slaughterhouse species, have high clinoid bones which rip into the relevant part of the hypothalamus on its removal. "To this day it is a mystery to me why Schally chose pigs," says Guillemin. Schally's reason is simple: "Because Guillemin was working with sheep. I had to accept as a theoretical possibility that he would come up with a hormone first, and if I were working on sheep too my contribution would be worthless."

A major boost to Schally's efforts came from the meat-packer Oscar Mayer and Company, which donated a million pig hypothalami. The money that would otherwise have gone to buying hypothalami could now be spent on staff, significantly compensating for the smaller size of the Schally team's budget compared with Guillemin's. "Guillemin was paying 40¢ a hypothalamus but I could pay all my money for salaries," Schally observes without regret.

The early 1960's saw Guillemin and Schally building up independent teams



Andrew Schally

and applying the lessons learned from the fruitless search for CRF to other presumed brain hormones. The two teams had different but probably roughly equal strengths and advantages. Schally had less money but a steady source of support in the Veterans Administration; Guillemin, apart from one multimillion-dollar contract from the Agency for International Development, had to compete with other researchers for grants from the National Institutes of Health. (For the last several years Guillemin has had $650,000 a year for his laboratory, Schally $350,000; in the late 1960's each had somewhat less.)

Guillemin left Houston in 1970 for the Salk Institute in La Jolla, California. The Louis Kahn-designed palace overlooks the Pacific in a site far from the madding crowd. Schally's team, by contrast, works in the concrete jungle of downtown New Orleans, squeezed in between the superdome on one side and a tangle of overhead freeways on the other.

Praise for the Other's Chemist

Both Guillemin and Schally created teams of high caliber. Guillemin's included Roger Burgus as his chemist and Wylie Vale as his physiologist, both of whom are still with him. Burgus, who succeeded Schally, was a student of Guillemin's first chemist, Walter Hearn. Schally's physiologist is Akira Akimura, and he has collaborated with Abba J. Kastin, also of the VA hospital in New Orleans, and with Cyril Bowers of the Tulane University School of Medicine. Tommie Redding and Weldon Carter have given him long-time biological help. For chemists, Schally has collaborated with Karl Folkers, of the University of Texas at Austin, and at a crucial time he had two Japanese scientists working with him, Yoshihiko Baba and Hisayuki Matsuo. The isolation programs put particular responsibility on the chemist, who has to be right up with the current state of the art. Guillemin and Schally each have high praise for the other's chemist. Matsuo, says Guillemin, is "a man for whom I have unlimited respect." Burgus, says Schally, "did tremendous, beautiful work."

The first new targets of the two teams were the hypothalamic hormones known as TRF and LRF. Like the elusive CRF, each was assumed to be the agent which induced the pituitary gland to activate particular hormone systems. TRF, thyrotropin-releasing factor, allegedly elicited the production of thyrotropin, the substance which in turn directs the thyroid gland to secrete the hormones which assist in regulating the body's rate of metabolism and temperature. Likewise LRF, luteinizing hormone-releasing factor, plays a similar role with respect to the system of hormones that control the body's reproductive functions.

Doubts About Competence

The two teams set to work. To endocrinologists watching their progress, results were strangely slow and disappointing, just as they had been during the quest for CRF. In 1966 the Schally team reported that pig TRF contained the amino acids glutamate, histidine, and proline in equal amounts. But they accounted for less than a third of the molecule's apparent weight and the rest seemed not to consist of amino acids at all. Schally possessed less than 3 milligrams of the material—the product of extracting 100,000 pig hypothalami—which was not enough to take the analysis further. He put TRF to one side and turned to LRF and other hormones.

By 1968, the two teams were working as furiously as ever but a crisis of confidence was developing among outsiders. Guillemin and Schally had each spent 7 years searching for CRF and another 6 in the hunt for TRF without any definite results. "People were becoming very skeptical," says Joseph Meites, one of the pioneers of the field. "There were questions about Guillemin's and Schally's skills, and many people still had doubts about whether these things actually existed in the brain."

The doubts came to a focus in the Endocrinology Study Section, the committee of scientists which advised the National Institutes of Health on which projects in the field should be funded. "Knowledgeable hormone chemists on our committee were saying, 'Why should we continue to support these men when they are not coming up with anything definite?' " Meites recalls.

To answer that question, the Endocrinology Study Section convened a sort of trial by jury under the guise of a scientific conference held at Tucson, Arizona, in January 1969. The Guillemin and Schally teams were invited to give progress reports before a carefully picked audience of experts in related fields. "Their support was on the brink because they were chasing each other rather than the real problem. The NIH wanted to use the audience's reaction as a means of assessing whether or not to go on funding the field," says Murray Saffran, a member of the study section at that time. The accused were not explicitly informed of the Damoclean nature of the meeting, but they were well enough aware that events had reached a critical pass.

The Tucson conference was one of the turning points of modern endocrinology. What in large part made it so was a finding which Guillemin, after 14 years of effort, reached just 3 weeks before the conference began.—NICHOLAS WADE

Next week: The 3-lap race to Stockholm.

Navy Meeting Drifts on a Sea of Unanswered Questions

Top level Navy brass, other government officials, and prominent civilians met at the Naval War College in Newport in late March to discuss the Navy's future. More important than the meeting's failure to resolve anything (what meeting does, after all?) was the sheer scope of disagreement on fundamental issues. Indeed, the number of problems the Navy is working on led one Air Force officer present to remark on the Navy's willingness to air its troubles publicly, before Congressional staffers, the press, business leaders, and other members of the military. "We have our problems too," he said, "but we try to keep them to ourselves."

The present crisis stems from the fact that the country sank some $150 billion—the preponderance of its defense spending—into Vietnam, mostly to pay for soldiers, logistics support, munitions, and the like. During that time, the Navy obtained rather little for capital investment in across-the-board modernization. The winding down of the war and the decrease in the defense budget in the early 1970's continued the trend. So today, many Navy officers are alarmed by the age and small numbers of Navy things—ships, planes, submarines, antisubmarine warfare systems, and even mines.

None of this would be a problem if funds were available to buy more equipment. But opposition in Congress, a stern attitude by the Carter Administration and high inflation have prevented the Navy from getting all the money it wants and from buying as much as it needs with the dollars it has. Thus the stage is set for a major, sometimes bitter debate in Washington—which spilled over to Newport—about the Navy's future.

Indeed, the importance of the Newport meeting was emphasized when the Administration used the occasion to deliver a stiff warning. Edward Jayne II, associate director of the Office of Management and Budget (OMB) for national security affairs, told the Navy that if it didn't "get its act together" by this time next year on its outstanding shipbuilding claims (which total $2.7 billion and involve one key yard that has threatened to stop work until the claims are settled), the President will favor the Air Force and the Army in the next budget. Jayne told his uncomfortable audience that the shipbuilding claims had already been the "single most prominent reason" why President Carter had declined to give the Navy added funds for new ships in the fiscal 1979 budget, now before Congress.

But shipbuilding was only one of an awesome range of problems discussed; among them were:

▶ *The global Soviet Navy.* During the Vietnam period, Soviet production of ships, submarines, and antiship planes and missiles rose unchecked. Today the Soviet Navy, once an inconsequential coastal force, can operate in the major oceans of the world, creating a new threat to the United States. As Navy Secretary W. Graham Claytor, Jr., noted, for the first time in 30 years the United States "faces a capable opponent at sea in the Soviet Navy." Helmut Sonnenfeldt, who formerly served as an adviser to Kissinger, provided the political underpinnings to this situation by saying that it was here to stay: even if the Soviets respond to Western pressures on their internal policies they will continue to seek to have a global military reach. Finally, the Soviet Navy's precision weapons, such as its antiship cruise missiles, have led critics to say the carriers are vulnerable and the Navy to argue for more money—such as for the $900-million-per-ship Aegis system—to keep the carriers secure.

▶ *Third World Intervention.* In addition to the Soviet problem, Navy leaders believe their forces must be ready to fight in Third World conflicts, such as that smoldering now in the Horn of Africa. The Navy must be prepared, as Undersecretary R. James Woolsey said, to conduct operations "on, under, above, and along the shores of 70 percent of the earth's surface"—a rationale used to justify bids for more ships and planes. But the Navy's critics, a few of whom were at the meeting, say that for these conflicts against mere Third World powers, the Navy does not need the most sophisticated and expensive systems.

▶ *Fleet size.* No one can agree on what size fleet the country should have, a problem that leaves both strategic planners and shipbuilders in the lurch. The week before the Newport meeting, President Carter signed off on a 5-year shipbuilding plan for the Navy, which would increase the force from its present level of approximately 450 ships to 525 by 1985. It called for maintaining a fleet of about 500 ships through the end of the century. But "Seaplan 2000," a major Navy study released at the meeting, illustrated the Navy's higher aspirations by concluding that 585 would do just fine. It all sounds like so much bean counting until one realizes that a single carrier group, consisting of a new carrier, four nuclear escort ships and two protective submarines, costs $7.2 billion—not including other support ships and aircraft.

▶ *Manpower.* As ships, planes, missiles, and anti-missiles become more sophisticated they require better trained