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FROM PHYSIOLOGIST TO PHARMACOLOGIST— PROMOTION OR DEGRADATION? FIFTY YEARS IN RETROSPECT

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When I studied medicine in the thirties at the University of Lund, an old provincial university in southern Sweden, pharmacology was a neglected discipline carrying on its activities on the outskirts of physiology. And to be sure, most pharmacologists of the time, with illustrious (notable) exceptions, expended their efforts on rather unimaginative, qualitative studies of the actions of drugs on animals and isolated organs, the classic targets of physiological research. Trained pharmacologists were nonexistent at Lund—they were rare birds in the whole of Scandinavia—and the pharmacology chair was held by a young physiologist with an interest in tissue respiration, which he studied with the Warburg and methylene blue techniques, in those days the highest fashion in metabolic research. To enter an academic institution a student had to serve as an unpaid assistant, an apprenticeship that could last for months or years. Such positions were very popular, with professors because they meant cheap teaching and research assistance and with students because they could mean the beginning of an academic career. Usually students who had done well on their examinations were offered these jobs. Since there were only about 20 students in our annual courses, the clever ones were chosen before they reached the pharmacology course, the last course of the three preclinical years. In my case, however, even after the pharmacology examination no professor offered me a position, so in desperation I took the rather unconventional step of asking for permission to begin in pharmacology.

My mind was not ready for a scientific career, however, and after one or two years of half-hearted contributions—I collaborated in some minor papers—I left science, temporarily as it turned out. Even though my scientific achieve-

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ments during these early years in pharmacology were negligible, I made a contact that was of the utmost importance for my future. Into the little university town a young man arrived one day in answer to an invitation. His name was Georg Kahlson—generally called G. K.—and he was to become a very disturbing and at the same time stimulating member of the little medical faculty. G. K. was preceded by his reputation as an outstanding scientist, with ten years of scientific education in Jena and Göttingen. When he arrived in Lund with his very charming and beautiful wife, Louise, and their fox terrier, Grock, he was received with great expectation. Once he was installed in the department of pharmacology, I found him a stimulating teacher, a generous supporter, and a very good friend. He was to remain all these things to me until personal differences separated us several years later.

G. K. influenced my scientific career considerably. In 1938, when he was appointed professor of physiology in Lund, he invited me to join his staff and I accepted. I stayed in his department for almost 15 years and held a chair in physiology from 1949 to 1953 until I returned to pharmacology, this time in Stockholm, as will be described below.

It is interesting to note the absence of distinct boundary lines between physiology and pharmacology in the middle of the century. The three Swedish chairs in pharmacology were held by physiologists by training: Gunnar Ahlgren at Lund, myself in Stockholm, and Ernst Barany at Uppsala. Of the three Swedish professors in physiology two were trained pharmacologists: Ulf von Euler in Stockholm and Georg Kahlson in Lund. Today trained pharmacologists sit in all the pharmacology chairs in Sweden, at present more than a score of them.

During the thirties the German cultural influence was still very strong in Sweden, as it was in all the Scandinavian countries. Most medical text books were in German and the scientific journal, *Skandinavisches Archiv für Physiologie*, was published in German. Practically all visiting lecturers were from German-speaking countries; few professors and students could follow a lecture in English or French. In this way we were isolated from the English-speaking scientific world before the last world war. With the war things changed rapidly.

As was customary at that time, my work with Kahlson included a scientific problem whose investigation might become a dissertation. Neurophysiology was developing rapidly. Erlanger & Gasser had received the Nobel Prize in 1944 in physiology or medicine "for their discoveries relating to the highly differential functions of single nerve fibers." The relationship between the thickness of a nerve fiber and its excitability afforded the possibility of selectively exciting the fibers with electrical stimuli of selected characteristics. At that time little was known about nervous control of the acid- and pepsin-secreting glands of the gastric mucosa. I was to attack this problem by the selective activation of vagal fibers and was sent to Ragnar Granit at Karolinska

Institute in Stockholm for guidance. Granit was considered a coming man in neurophysiology: with Hartline & Wald he became Nobel Laureate in 1967 "for their discoveries concerning the primary physiological and chemical visual processes in the eye." I spent six months with Granit while one of his engineers worked on constructing a stimulator that would deliver all kinds of impulses—triangular, rectangular, circular, for example—of varying duration, frequency, steepness, etc. Time went by, the apparatus became more and more complicated, and its completion was repeatedly delayed. I became impatient and returned to Lund. There while waiting for the stimulator I began some basic experiments for practice. With an induction coil yielding an alternating current of about 40 periods per second and a metronome for the rhythmic alternating stimulation of the cat's vagus nerves with about one impulse volley per second, I was able to obtain a profuse gastric acid secretion that lasted for hours. In fact, my stimulation technique was a direct copy of the one described by Pavlov at the turn of the century.

What to do next to fulfill my professor's expectations? An accidental observation answered my question. Suddenly my experiments failed; vagal stimulation no longer aroused gastric secretion, and I realized that in order to improve the collection of gastric secretion I had ligated the pyloric area and probably interfered with the antrum vascular supply. Further analysis showed that interference with antrum function either by cocainization of the antral mucosa or extirpation of the antrum abolished or strongly reduced the secretory response to vagal stimulation. Pavlov had already observed that cocainization of the antrum of dogs blocked the gastric secretory response to feeding or sham feeding. He assumed the effect to be due to paralysis of antral secreting reflexes. In 1906, however, Edkins presented his "gastrin" theory according to which gastric secretion was under the control of the antral hormone gastrin, similar to the way pancreatic secretion was controlled by secretin, as postulated by Bayliss & Starling a few years earlier. Edkins's gastrin theory was never accepted by his contemporaries and more or less died. The American physiologist Ivy denied the existence of gastrin in numerous articles and considered histamine the sole humoral agent operating to control gastric secretion.

I postulated that my manipulations with the cat antrum area in some way had interfered with the gastrin mechanisms and I tried to prove it in cross-circulation experiments between two cats. The recipient cat had a cocainized antrum and no gastric secretory response to vagal stimulation; the antrum of the donor cat was intact. As I had observed earlier, vagal stimulation in the recipient cat did not evoke gastric secretion, but in the donor cat, to my delight, gastric acid flowed, indicating the presence of a blood-borne secretagogue.

Current American scientific literature was hard to come by at Lund, but about this time, I happened to come across a proceedings abstract by Komarov, a pupil of Pavlov who had emigrated to the U.S.A., in which he described the

extraction of a secretory principle from the dog's antral mucosa. Komarov assumed this principle to be identical with Edkins's gastrin. I made similar extracts from the cat's antral mucosa and found that, even though such extracts did not evoke gastric secretion in cocainized cats, the accompanying infusion of such "gastrin" preparations and vagal stimulation induced profuse gastric secretion. These observations were presented in my thesis, "The Part Played by the Pyloric Region in the Cephalic Phase of Gastric Secretion" (1942), in which I postulated that gastrin was released by vagal impulses and that gastrin and vagal impulses in some way potentiated each other's effects. Unfortunately, radioimmunoassay (RIA) had not been invented at that time and the occurrence of gastrin could not be directly proven, but shown only indirectly as a gastric secretory response. It would take more than 30 years for my daughter Kerstin and I, using an RIA worked out by Berson & Yalow in New York, to directly demonstrate the vagal release of gastrin in cats.

My thesis, published as was customary as a monograph, met with strong criticism and was passed by the faculty only after several stormy meetings. The criticism with which the faculty at Lund received my thesis hurt me very much, it is true. But what almost broke me was the negative attitude I met abroad. When his gastrin theory was rejected, Edkins left science, married his laboratory assistant, and dedicated his life to university politics. I felt inclined to follow his example, but I resisted the temptation and fought on.

I have dwelled so long on the problems surrounding my dissertation because they illustrate a situation common to young scientists in those days. Young scientists were at the mercy of one or a handful of professors who were quick to criticize and loathe to praise. Most young scientists need positive criticism and encouragement, and my chief, G. K. gave me these. With his support I decided not to give up and become a practitioner, but to continue my research despite the criticism with which it had been received.

Although Sweden was not drawn into World War II, the war period meant almost total isolation from the outside world. Foreign scientific journals—especially English-written ones, of course—arrived only occasionally. At the end of the war, a number of Danish scientists of Jewish birth fled to Sweden and found refuge at Lund. Among them were well-known physiologists like August Krogh and Fritz Buchtal. Despite the unfortunate circumstances under which they came, they brought fresh air and a fighting spirit to the somewhat musty atmosphere of the little university town.

Once the war was over and the borders opened again, Swedish scientists hurried abroad. Now, however, their destinations were not Germany and Great Britain, both devastated and impoverished by the fighting, but to the undamaged and prosperous United States. Since I had been working on gastric secretion, it was natural that I choose to study with a specialist in gastric physiology. In those days, there were two alternatives: Ivy, whose laboratory

was at Northwestern University in Chicago, and Babkin at McGill University in Montreal.

Ivy was a student of a famous Swedish physiologist, Anton Julius Karlsson, who was still alive at that time. Babkin was a Russian refugee, a student of Pavlov. I chose to work with Ivy, unfortunately, as it turned out, inasmuch as I got neither education nor ideas from him. Ivy was a hard worker. One found him at his desk practically day and night, Sundays as well as weekdays. He had many young scientists in his laboratories but rarely appeared there himself. These young guests were all working busily by themselves in some corner on problems Ivy had given them. He took their reports and wrote papers on their findings. My ticket of admission was to demonstrate my technique for the isolation of gastrin and its secretory activity. For that purpose, I was given a little dark closet, 2 × 2 m, without a window or equipment. Evidently, no one had worked with a cat in Ivy's laboratory before, and it took months to get the necessary equipment, in fact very simple things, not to mention getting cats. Since I had no technical assistance, my wife helped me, very bravely indeed since she had never set foot in a laboratory. When after a few months I had prepared my first gastrin extracts and could demonstrate their secretory effect on the cat's stomach, I called for Ivy. He had lost interest by that time, however, and flatly denied that the secretory effect could be due to gastrin. Instead he insinuated that it was due to contamination with histamine.

My main purpose in visiting Ivy's laboratory was to have an opportunity to work with conscious dogs. Ivy was especially famous for his studies on pouch dogs. In some preliminary experiments in Lund I had observed that the gastric secretory response to sham feeding of dogs was inhibited by antrectomy. I wanted to confirm these preliminary observations. However, the dogs at Ivy's laboratory—stray dogs caught by the Chicago police—were so filled with lice and the animal quarters were so filthy that I could not allow my wife to work there. Without assistance in the operative procedures I had to give up. After some months Ivy left his laboratory to assume a position in physiology at the University of Illinois. I felt forsaken and began looking for other scientific contacts at Northwestern.

One day I passed a laboratory in which a bald, kind-looking man was sitting bent over his desk. His name was Horace W. Magoun and he was well known for his experiments with stereotactic instruments, with which he could stimulate well-defined areas in the brain. I went in and asked if I could work in his laboratory. He was busy writing a book, he said, but I was welcome to practice with his instruments. I did so and, lacking any real idea of what to do, I put the electrode into the hypothalamus of a cat. To my surprise, the stimulation induced blood-pressure fall and bradycardia instead of what I expected, blood-pressure rise and tachycardia. My curiosity was stimulated and I continued for a few weeks just mastering the technique. The small observations I made were

presented with the kind help of Magoun in the proceedings of the Society of Experimental Biology and Medicine.

In another corridor I found pharmacologist C. A. Dragstedt, who was well known for his studies on the role of histamine in anaphylactic reactions. He and Magoun were my first important contacts in the American scientific community. With their help I made many American acquaintances who would be of the greatest importance for my career, and a few months later, after a tour around the country, I left the States.

Back in Lund after the year abroad, we started enthusiastically to explore the possibilities of Magoun's stereotactic instruments. I was very lucky to have as my collaborator a very able young man, Björn Folkow, who later became professor of physiology in Gothenburg with an international reputation for his studies on circulation and hypertension. Our first experiment hit an area in the hypothalamus of the cat—later defined as the defense area—from which a specific reaction pattern, including rather selective vasodilator responses in the skeletal muscles, was induced. We had discovered what was later described as a cholinergic vasodilator outflow in the sympathetics. We worked happily for several years on the distribution and function of this cortico-spinal vasodilator outflow to the skeletal muscles of the cat and dog. We had (to us) exciting skirmishes with the Nestor of British pharmacology, J. H. Burn, who for many years had defended the existence of adrenergic vasodilator fibers. His main argument was the well-known vasodilator action of adrenaline on the skeletal muscle blood vessels. After reciprocal laboratory visits the dispute was settled and the existence of cholinergic vasodilator fibers recognized.

Our vasodilator research led successively to extensive studies on central and peripheral nervous vasomotor control. Both in Lund and later in Stockholm many dissertations were published in this field. I would like to mention two students, Percy Lindgren and Sune Rosell, who were my collaborators in Stockholm for many years. We found later that the vasodilator action of adrenaline occurring after intravenous injection is transformed into vasoconstriction upon stimulation of sympathetic nerves depleted of their noradrenaline by reserpinization and then reloaded with adrenaline. Apparently, the adrenaline released by sympathetic nerve stimulation hits vascular receptors different from the receptors stimulated by adrenaline given intravenously.

Concomitant with these scientific events, things were happening on the political front. G. K. was very active in the developments to come. In large part due to his forceful propaganda and his good relations with influential members of the sitting Social Democratic government, a Swedish Medical Research Council was formed patterned after the corresponding British organization. Increased resources were given to natural science and medical research and new chairs were instituted at the national universities. As a result of this new commitment to research, Sweden took the scientific lead in Scandinavia, and

in some disciplines Swedish scientists have reached the international forefront.

I was lucky enough to profit from these favorable developments and was appointed to the new chair in physiology at Lund University. Plans were also developed to build a new physiology department at Lund and, as G. K.'s favored assistant, I became deeply involved in preparatory negotiations with governmental authorities, architects, contractors, and others. Building began, but I was never to move into the new laboratories. The partnership with my old teacher and benefactor came to a sudden end. I was made uncomfortable by this development and looked for a way out. What I found changed my life. The chair in pharmacology at Karolinska Institute had been vacated with the retirement of Göran Liljestrand. I applied for the position and to my relief—and to the disappointment of others—I was invited to Stockholm in the summer of 1953.

Karolinska Institute was a new world to me. The faculty for generations had been composed of eminent and forceful scientists enthusiastically and successfully engaged in developing the institute into a scientific medical center of international repute. To sit on this faculty was a tremendous opportunity for a young professor in pharmacology. My predecessor had been a very forceful and influential member of the faculty, but he was not to witness the great expansion in the science of pharmacology waiting around the corner. I was the lucky one who entered the scene at the right moment.

In the stimulating atmosphere of Karolinska Institute, with its recognized international position, I was able to recruit a group of enthusiastic young collaborators within a few years. The competition among disciplines for young talent was tough, and pharmacology was the last course in the preclinical curriculum—two months at the end of the third year. But I had a few tricks to help to attract some of the better students. One I had learned from G. K. in Lund. On his initiative there we bought a sailing boat for the use of staff members and their groups. It was a 40-foot sailing yacht especially built for sailing in the Swedish archipelago. Since histamine was one of the main interests in our department, the ship was named the *Histamina* and its dinghy the *Histaminase*. From the masthead flew our ensign, in honor of our favorite experimental animals two red cross-laid cats on a white ground. Many agreeable summer adventures at sea created a feeling of solidarity and a community of interests among us that were of great value during the everyday activities of the rest of the year.

When I took over the pharmacology department in Stockholm, I repeated the trick. With some friends I bought a sailing vessel, this time a rather large one that could accommodate quite a few people. It was a 30-ton revenue cutter that we rebuilt ourselves into a ketch, with three foresails on a long bowsprit. It was both fast and easy to maneuver. Many young pharmacologists got their training

in seamanship on board this ship and our adventures were legion. I remember especially a trip to Åbo in Finland in 1966, where the 12th Scandinavian Congress for Physiology was to be held. We left Stockholm in fine weather with 12 Swedish scientists on board. We never reached Åbo, however. Instead we ran into a hurricane and almost went down, but we found a port of refuge and some leading members of Sweden's scientific community survived to continue their work.

The Department of Pharmacology in Stockholm was relatively new. It was built in 1948 when Karolinska Institute moved from its old site close to Stockholm's center to its new grounds at Norrbacka just north of Stockholm. Unfortunately, the original building plans had for economic reasons been reduced by 50% and as a result the animal quarters and the laboratory equipment, among other things, did not fulfill modern requirements, at least not in my opinion. My first step as chairman was to deliver an address to the faculty in which I presented the future of pharmacology as I saw it. I anticipated the development of various fields of pharmacology, such as biochemical pharmacology, neuropsychopharmacology, clinical pharmacology, and toxicology, and recommended the eventual establishment of chairs in these fields. I also asked for the immediate enlargement of the pharmacology department, especially its animal quarters, and for money to modernize the equipment. Many faculty members shook their heads at this presumptuous newcomer, but I must say to their credit that they were very cooperative; two decades later my demands were fulfilled in good measure, including chairs at the institute in all the subdisciplines I had mentioned.

In retrospect, the pharmacology department at the institute seems to have developed rather smoothly, but at the time some of our victories seemed hard won. Especially difficult was convincing the Ministries of Education and Finance to support our growth. I remember particularly the resistance that met our plans to enlarge the department. When the ministeries rejected even our request for a barrack to be used as temporary animal quarters and erected at our own expense, we were discouraged. But the stricture "that any animal quarters, even temporary ones, should be removable without any delay in case the grounds were requested by the building board for other purposes" gave us an idea. We bought circus wagons from the Stockholm amusement park—the original horse-drawn ones—equipped them with cages for rats, cats, and dogs, painted them bright red with white windowframes, and placed them in a semicircle outside the pharmacology department. This anachronistic sight aroused the public and angered the government authorities. They never forced us to remove the wagons, however, and after a few years of publicity in the leading newspapers we were allowed to build not only new animal quarters but new laboratories. The next problem was equipment. Fortunately, generous support from the National Institutes of Health saved us. In this context, I want

to emphasize that financial help from the U.S. in the two decades after the war was of inestimable value in expanding the institute's scientific activities during these years. Unfortunately, Swedish political concerns forced a gradual decline in U.S. financial support. In fact, for a time such support practically disappeared.

Another important force in the development of Karolinska's scientific potential has been its participation in the Nobel Prize Awards in physiology or medicine. In the beginning the institute was reluctant to accept the responsibility, but over the years it has been very well managed and put to profitable use. Serving on the Nobel Committee, as I have done for decades, is an inestimable opportunity to watch international scientific developments. Moreover, studying the achievements of eminent colleagues has been both rewarding and stimulating to my own ambitions.

As I mentioned earlier, of primary interest at the Department of Physiology in Lund in the 1940s was histamine. This amine has intrigued physiologists since its synthesis by Windaus & Vogt in 1907, but its functional role was and still is obscure. Histamine was known to be distributed in tissues all over the body but its precise localization or mode of storage was still unknown, although it was believed to be stored in some way chemically linked to protein. The new extraction technique elaborated by Charles Code at the Mayo Clinic raised new expectations among histamine enthusiasts, but it had still to be assayed biologically on the guinea-pig ileum, which had been found to be especially sensitive to it. This biological assay was both time-consuming and tedious and I felt sorry for my young colleagues, who spent their time on these boring assays. I had resisted all invitations to join the histamine gang, but by the time I arrived in Stockholm things were changing. Chemical techniques had been developed for determining histamine, specific histamine releasers like compound 48/80—discovered by MacIntosh & Paton in 1949—had appeared, and histamine was found to be localized in mast cells by Riley & West in 1953.

Ever since my "gastrin period" in Lund, storage and release phenomena had spurred my interest. How could biologically active substances be stored in an inactive form and "reactivated" immediately on release? In our laboratory cat consumption was high but the rewards were considerable. To make better use of the animals, we decided to perfuse cat limbs in histamine-release studies. Cat skin turned out to be very rich in histamine, as well as a rich source of slow-reacting substance (SRS), so-called because it induces a slow contraction of guinea-pig ileum. SRS was known to accompany histamine release in anaphylactic reactions and was assumed to be at least partly responsible for anaphylactic symptoms. During the 1960s and 1970s we studied the chemical and biological characteristics of cat SRS, and quite a few young scholars defended their theses on SRS problems. We had an almost pure SRS preparation, its UV spectrum identified and ready for mass-spectrographic study,

when Samuelsson and his group very elegantly solved the problem and developed the now well-known leucotriene hypothesis that won him the Nobel Prize in 1982. Samuelsson isolated leucotrienes from leucocytes, but in my mind there is no doubt that the cat SRS belongs to the leucotriene family.

Parallel with our research on SRS, our study of histamine developed nicely. Since histamine is located in mast cells, a rational approach to problems concerning its storage and release required access to isolated mast cells. Somewhat pure suspensions of rat mast cells had been obtained by gradient centrifugation of mixed cell populations from rat peritoneal washings on sugar. Unfortunately, such cells, although morphologically seemingly intact, were insensitive to compound 48/80 and other histamine-releasing agents. In our search for other density gradients we decided to try dextran, but by mistake the pharmacological company delivered ficoll. This new polymere turned out to be an excellent gradient material and we were able to obtain up to 95% pure mast cell suspensions. Bertil Diamant, now professor of pharmacology in Copenhagen, many other young collaborators, and I experimented with these mast cells.

In the beginning, our interest focused on the mechanism of mast-cell response to "degranulating" agents like compound 48/80 and antigens. The dependence of the response on oxidative and glucolytic energy production and the role of ATP in the release process were among the questions studied. We theorized that lecithinase A (later phospholipase A) played a role in an initial step of mast-cell reaction. Recently, phospholipase A activation has again been the focus of attention, this time as one of the initial processes in release mechanisms.

As years went on, our interests shifted from mast-cell response to the mechanism of histamine storage and release in mast-cell granules. We observed one day that granules isolated directly from mast cells lysed in deionized water still contained histamine but that they immediately lost their histamine when suspended in salt solutions like 0.9% NaCl or serum. This observation indicated to us that the histamine in the granules was stored in weak ionic linkage to the granule matrix and was then released by cation exchange once the granules were exposed to cation-containing media. For the next 20 years we were spellbound by the idea that the storage and release not only of histamine but also of other biogenic amines and other charged substances, for example neuropeptides, might be effected according to the cation-exchange principle.

The idea that histamine is stored in ionic linkage to anions in mast-cell granules was not original. The presence of heparin in the granules led early to the assumption that histamine is stored in ionic linkage with this strongly acid polysaccharide. We soon found that this was a premature conclusion, however. An analysis of the binding properties of isolated granules showed stoichio-

metric relationships and pH-dependence, for example, indicating histamine's ionic binding not to the sulphated groups in heparin but to the carboxyl groups. Chemical analysis of the granule matrix, as well as quantitative studies of the storage capacity of isolated granules and of "artificial granules" (a heparin-protein complex) supported our idea that histamine is stored in ionic linkage to carboxyls in a protein-heparin complex in which the sulphated groups of heparin are masked by strong ionic binding to the amino groups of the protein. The fact that histamine is bound in weak ionic linkage to protein carboxyls and not to the strong acidic groups of heparin was an essential observation of importance for our later speculations about the cation-exchange process as a general principle in storage and release mechanisms.

Quantitative studies of the storage capacity of mast-cell granules for histamine and sodium, the stoichiometric relationships between sodium uptake and histamine release and other questions led to the conclusion that in vitro mast-cell granules behave as weak cationic exchangers with carboxyls as the ionic binding sites. Electron microscopic studies strengthened our belief that the release of histamine from the "degranulating" cell also occurs as a cation exchange sodium $\rightleftharpoons$ histamine. Later, a closer inspection of our electron microscopic pictures—the result of a collaboration with the eminent Hungarian specialist Pal Röhlich—cast some doubt on the current idea that degranulation of the mast cell is a primary and histamine release from the expelled granules a secondary step in the release response. Through electron microscopic autoradiography we observed that granules in the periphery of the cell may swell and loosen their histamine in spite of the fact that they have not yet lost their membranes. In other words, the electron microscopic pictures indicated that histamine release—probably by cation exchange across membranes with increased permeability or through newly formed pores—might occur as the primary step, with the expulsion of granules a secondary phenomenon. I mention this observation because I later defended the idea that the release of neurotransmitters might occur not as an exocytosis but as a fractional release of the transmitter by cation exchange initiated by the nerve impulse. I will come back to these recent studies below.

The observation that led to the idea of cation exchange being a general principle of amine storage and release was the observation that mast-cell granules in vitro take up not only sodium and histamine in a competitive way, but also other amines, biogenic as well as synthetic, as long as they contain a charged amino group. All these amines, among them the transmitter amines noradrenaline, adrenaline, dopamine, serotonin, and acetylcholine, seemingly compete for the same ionic sites in the mast-cell granules and are released by sodium and other inorganic cations. Therefore might the matrix of other amine-storing granules also have properties similar to cation-exchanger materials?

So far we have studied chromaffin granules and adrenergic nerve granules from this point of view. We discovered that the matrices of these two types of granules show properties reminiscent of cation-exchanger materials, with carboxyls as the ionic binding sites. Of special interest to us were experiments that demonstrated great similarities in the cation-exchange properties of the synthetic carboxyl resins, e.g. the Amberlite IRC-50 and Sephadex C-50, and the matrices from these granules. When the synthetic resins and isolated granules from chromaffin cells and nerves were exposed to isotonic NaCl by superfusion, the release of catecholamines and noradrenaline showed the same kinetics. Recently, the in vivo release of catecholamines from cat and pig adrenals induced by supramaximal splanchnic nerve stimulation shows the same kinetics observed in vitro. At present, we are looking for further evidence that the storage and release of transmitter amines follow the principles of cation exchange and that the transmitter release and perhaps the release of other amines and neuropeptides occur not by exocytotic emptying of a few granules but by cation exchange as a fractional release from multiple granules.

The modern and roomy animals quarters approved by the authorities in the face of our circus wagons provided the facilities for gastrointestinal research on conscious animals. Gastrin research began to see movement again with the important contributions of C. A. Dragstedt, previously professor of surgery in Chicago, who was very active after his retirement in experimental gastrointestinal surgery in Gainesville, Florida. He manipulated the dog antrum surgically and found that excluding the antrum either as a separated pouch or as a transplant in the colon led to a hypersecretion of HCl in the remaining stomach, frequently followed by penetrating peptic ulcers. This hypersecretion disappeared when antrum mucosa was acidified or extirpated. Dragstedt considered that the changes in HCl secretion he observed reflected disturbances in the gastrin mechanism, since gastrin release from the antrum is inhibited by acid pH.

These findings revived my old interest in gastrin and we decided to confirm and if possible extend the observations I had made in Lund that the acid secretory response to sham feeding disappears after antrectomy. My young collaborator, Lars Olbe, did an excellent job in conducting the experiments. He invented an esophagal cannula of plastic that allowed the dogs to feed themselves and survive in good health for years. Olbe found not only that antrectomy practically terminates the acid secretory response to sham feeding but also that intravenous infusion of subthreshold doses of gastrin *during* sham feeding induces a dose-dependent acid secretory response. In other words, my previous observations on the interaction between gastrin and vagal impulses in anesthetized cats were fully confirmed in conscious dogs.

There still was no technique for determining gastrin in the blood, but it would come soon. Solomon Berson & Rosalyn Yalow reported in 1955 that they had

developed antibodies against insulin and had used them to develop a radioimmunoassay. Their report caused a sensation, since it was considered impossible to induce antibody production against such small protein molecules. In fact, a respected scientific journal refused to publish Berson & Yalow's first paper unless they changed the term *antibody* to a more neutral term. Today everyone knows that Berson & Yalow were correct; their radiommunoassay for insulin revolutionized the whole polypeptide area. Unfortunately, Berson died unexpectedly of a heart attack—he worked himself to death—but Yalow was awarded the Nobel Prize "for the development of radioimmunoassays of peptide hormones" in 1977, a prize meant for both of them.

I met Berson before his death, when he gave the Ihre lecture at a Nobel symposium in Stockholm in 1970. At a dinner at Bengt Ihre's home I asked him to work out a radioimmunoassay for gastrin. He promised to try and a few months later he called me from New York to say that he had a gastrin RIA ready for me, would I come to New York to see it? Although I did not consider it possible to go myself, I sent one of my young pupils, Göran Nilsson. A few months later in Berson's laboratory, Nilsson and Berson were able to show that sham feeding induces a rise in plasma gastrin level. When the gastrin RIA was brought home to Stockholm, my daughter Kerstin, as already mentioned, demonstrated that vagal stimulation in the cat causes a considerable output of gastrin-17 not only into the blood but also into the stomach. Since then, in our laboratory as well as in others, researchers have shown that the vagus nerve contains several polypeptides—cholecystokinin, vasointestinal peptide, substance P, insulin, somatostatin, gastrin, and many others—that appear in the blood and gastrointestinal canal when the vagus nerve is activated. In fact, in addition to sham feeding, suckling leads to a hormonal release pattern with a concomitant occurrence of gastrointestinal and hypophyseal hormones, indicating an intimate central coordination between these hormonal delivery sources.

Our gastrin studies stimulated our interest in the role of the antrum-duodenum area in controlling gastric acid secretion. The Pavlov school considered this area a reflex center for the excitatory and inhibitory control of gastric secretion.

We were able to confirm previous observations that acidification of duodenal content leads to a pronounced inhibition of acid secretion in Pavlov and Heidenhain pouches. However, this inhibition does not occur until the pH is suppressed 2–3. Since such a low duodenal pH is never observed under normal conditions, the functional role of the duodenal inhibitory mechanism has been seriously doubted. However, between meals the stomach empties its acid content into the duodenum, and as a result there might be an acidity gradient with low pH close to the pylorus, the pH rising with increasing neutralization during the distal passage of duodenal content. Could the inhibitory mechanism

be located in the bulb and, if so, does bulbar pH reach the required low values? We found in fact that acidification of the duodenal bulb to pH 3–2 or lower does activate the inhibitory mechanism. Moreover, with a series of technically advanced surgical procedures it could be shown that the bulbar inhibitory mechanism is humoral. We baptized the unknown inhibitory principle *bulbogastrone,* but our attempts to identify it chemically in duodenal extracts failed.

In the meantime another of our colleagues, Sven Andersson, was sent to Los Angeles, where Morton Grossman of UCLA had perfected a technique with which it was possible to register the pH-gradient in the duodenum. They found that in both man and dog postprandial pH in the duodenal bulb decreases to 2–3. In other words, the bulbogastrone mechanism might play a physiological role in the inhibitory gastric acid secretion. Later my daughter Kerstin observed that acidification of the duodenal bulb leads to increased somatostatin levels in the peripheral blood. These levels are high enough to exert inhibitory actions. Whether bulbogastrone is identical with somatostatin remains to be established.

As is evident from this somewhat rhapsodic narrative, my scientific activities and those of my collaborators were physiological in nature. One is justified to ask what my department has done for the field of pharmacology. In fact, rather much.

The scientific staff in the Department of Pharmacology at Karolinska Institute has reached considerable size. Last year the list included four professors, four senior lecturers, four assistant professors, two adjunct professors (part-time scientists from the pharmaceutical industry), seven research fellows, and twenty-five postgraduate students. More than 150 scientific papers were published. Out of 80 postgraduate students who have defended their theses at the department in the last 30 years, 25 are professors of pharmacology or of related theoretical and clinical disciplines. Our research activities cover such diverse fields as biochemical pharmacology, cancer chemotherapeutics, prostaglandins, the physiology and pharmacology of adrenergic transmitter mechanisms and of purines, neurohumoral peptide physiology, the pharmacology of gastric secretion, dental pharmacology, and neuropsychopharmacology. If the two chairs in clinical pharmacology and one in toxicology are included—they have branched off to form their own departments—the scientific output is very high indeed.

I suppose such a large and diverse department reflects favorable developments in the pharmacological field, but at the same time the growth of huge departments with many independent research groups has its risks. The diversification of scientific interests can lead to in-fighting among special interests. Harmony and communication among individuals can be jeopardized. Without common goals, the strength and in the long run the future of the department are endangered. I have no solution to the problem, but I can recommend one rather

effective measure to prevent or at least retard such an undesirable development. This is the organization of what we have called a manuscript committee, whose members are the "grown up" scientists in the department. This committee reads and edits all manuscripts emanating from the department before they are published. Such a procedure is a great help to young researchers and effectively serves to uphold high scientific standards for the publications, since nobody—especially not the older professors—wants to present bad papers. What is more important, however, is that everyone gets to know what work is being done throughout the department, an effective measure against the isolationism and self-sufficiency that often occur in large organizations.

Teaching pharmacology to medical students, one was confronted with how little doctors, clinicians as well as practioners, knew about drugs. Refresher courses in pharmacology for doctors were instituted to rectify this situation, and such courses led directly to the development of clinical pharmacology, today a strong discipline in Sweden, with chairs and head positions at every teaching hospital in the country. In the beginning, clinical pharmacology met with scepticism, especially from internists, but resistance disappeared when clinical pharmacologists were relieved of their hospital duties to serve as teachers and advisers in drug therapy and drug research. It is still that way in Sweden, and the collaboration between clinicians and clinical pharmacologists is intimate and profitable.

The growth of the medicinal industry and the introduction of chemical and biochemical techniques after World War II opened up new ways to study the pharmacodynamic properties of drugs. Increased insight in the quantitative aspects of drug action on animals and man paved the way for quantitative drug therapy and the development of clinical pharmacology.

These new dimensions within pharmacology weakened the traditional ties between pharmacologists and physiologists. In fact, the new generation of biochemical pharmacologists and other scientists felt no loyalty to physiology at all. Physiologists and the older generation of pharmacologists, who had received their scientific training in physiology, did not seem to realize the explosive power of these new trends.

Except in the leading scientific communities in France, Germany, Great Britain, and the U.S., national pharmacological societies were formed slowly. Nationally and internationally, pharmacologists were represented by physiological societies and there was growing dissatisfaction among pharmacologists with their inability to influence the scientific program at physiology congresses.

In the 1950s, beginning at the 18th congress of the International Union of Physiological Sciences (IUPS) in Copenhagen in 1950, a special pharmacology day was arranged at the end of the meetings. At these gatherings, the question of an independent international organization of pharmacologists was repeatedly

put on the agenda. An international committee was set up with Corneille Heymans of Ghent as chairman and Carl F. Schmidt of Philadelphia as secretary. After nearly ten years of discussions and negotiations, IUPS in 1959 agreed to the formation of an independent division for pharmacologists within the organization, the Section on Experimental Pharmacology (SEPHAR). The agreement was a typical compromise. The constitution of IUPS was revised to authorize SEPHAR to "organize international conferences, symposia and congresses and to carry on other activities provided that they do not conflict with the aims and principles of IUPS." This objection led to an agreement that SEPHAR "would do its best not to compete with or otherwise weaken the triennial congresses of IUPS whenever it arranges separate international pharmacological programs." Carl Schmidt was elected the first president of SEPHAR, with Daniel Bovet as secretary. The SEPHAR council had its first meeting in Stockholm in 1961. Council loyalty to IUPS was demonstrated by its appointment of a liaison officer, E. J. Ariëns, as a member of the local organizing committee for the next physiology congress in Leyden in 1962. The council also decided to continue pharmacology day at future physiology congresses.

As years passed and increasing contacts with foreign colleagues widened my horizons, I could not avoid recognizing the increasing tension between physiologists and pharmacologists, as the repeated proposals for an idependent international pharmacological organization showed. The notion of holding an international meeting of pharmacologists in Stockholm was born over a drink in my home one fall evening in 1958. My friend Tom Maren, professor of pharmacology in Gainesville, Florida, and I were discussing the unsatisfactory international position of pharmacology. True, negotiations had by then begun to form a pharmacology division within IUPS. Even so, dissatisfaction was widespread, especially among biochemically oriented pharmacologists, who felt no community with physiologists and who wanted to break loose completely to organize their own scientific programs.

Tom Maren belonged to the group of young non-traditional biochemical pharmacologists who pleaded for the independence of pharmacology. Tom and I decided to make inquiries on the question among prominent friends and colleagues. The correspondence in my files reveals little enthusiasm and encouragement for the formation of an independent pharmacological association. Most responses were ambiguous or passive. Some were directly negative. Most felt that to break with the physiologists was a mistake; many predicted difficulty in raising the necessary funds.

In the meantime SEPHAR was officially established—not without opposition within the parent organization—at the IUPS congress in Buenos Aires in 1959. As mentioned above, according to the revised IUPS statutes, the new division was authorized to organize its own international meetings.

The formation of SEPHAR paved the way for international pharmacological activities. But when we in Stockholm undertook to arrange the first international pharmacological meeting, we were well aware of the divergences of opinion, not only about what form such a meeting should assume but even about whether it should be held at all. Some pharmacologists were enthusiastic advocates of an international pharmacological congress of the conventional kind. Others favored the organization of symposia. Lastly, there were those who rejected the whole idea. In particular I understood the apprehensions of those who felt that an international congress of pharmacologists would weaken the valuable communication between physiologists and pharmacologists long fostered by the international physiological conventions. As a physiologist by training I could well appreciate that point of view. However, like many others, I felt that the danger of a schism among the pharmacologists themselves was so great that some form of an international gathering should be arranged. A feasible compromise solution—at least for the time being—was to organize pharmacological meetings that would provide satisfactory interchange between older and younger generations and offer opportunities for contact not only with physiologists but with biochemists and representatives of other allied disciplines.

At a preliminary informal meeting in Washington early in the winter of 1959, I declared my willingness to arrange a pharmacological program in Stockholm. SEPHAR's agreement not to compete with the 1962 IUPS congress precluded emphasis on physiological presentations. The recent outstanding developments in biochemical pharmacology spoke in favor of a biochemical approach. We therefore decided to put together a series of symposia on the topic, "Modes of Actions of Drugs." One of the most active spokesmen for this program was Bernard B. Brodie, at that time head of the Department of Chemical Pharmacology at the National Institutes of Health in Bethesda, who gave us his enthusiastic and invaluable support from the beginning. K. K. Chen from the Lilly Company in Indianapolis was another indefatigable and influential supporter. C. Heymans of Ghent and C. Schmidt of Philadelphia, who joined when we were well embarked on the adventure, also gave full and unflinching assistance. Even IUPS contributed 2,500 U.S. dollars for preliminary expenses.

In spite of the efforts of the organizing committee to give the program an international character, scientifically as well as geographically, Americans clearly dominated the meetings. Five out of eight organizers and 478 out of 1483 attendees were Americans. In angry letters the Russians, French, Belgians, and others accused us of favoring or giving in to the Americans. The fact is, however, that the program committee's decision to emphasize biochemical pharmacology was more or less forced upon us by our agreement with the IUPS not to focus on physiology and the Americans, and to a certain extent the Germans, were the leaders in biochemical pharmacology at that time. This new

branch of pharmacology was still rather undeveloped in most European countries, especially in those where the complainers came from.

The Stockholm meeting was to become not only the first in a series of successful international pharmacological congresses and a strong impetus to the development of the field. It also led to the formation of the International Union of Pharmacologists (IUPHAR). IUPHAR was officially inaugurated by the General Assembly of the IUPS in Tokyo on September 2, 1965. The first ordinary meeting of the IUPHAR council was held in Sao Paulo on July 28, 1966. Since then seven IUPHAR congresses have been held, in Stockholm in 1961, headed by myself; in Prague in 1963, headed by H. Rašková; in Sao Paulo in 1966, headed by M. Rocha e Silva; in Basel in 1969, headed by K. Bucher; in San Francisco in 1972, headed by R. Featherstone; in Helsinki in 1975, headed by K. Paasonen; in Paris in 1978, headed by P. Lechat; and in Tokyo in 1981, headed by S. Ebashi.

Within IUPHAR, the divisions of clinical pharmacology and of toxicology demonstrate not only the growth of pharmacology as a field, but also IUPHAR's commitment to represent all aspects of the discipline, allowing new branches independence within the framework of the parent organization. With its membership in ICSU, WHO, CIOMS, and various other international scientific organizations, IUPHAR belongs to a global network of government, academic, industrial, and other organizations through which it exerts worldwide influence on all aspects of pharmacological research and teaching as well as on drug development and pharmacotherapy.

My years as secretary of SEPHAR and then as president of IUPHAR were a very challenging and profitable time, both scientifically and personally. My understanding has widened; my circle of friends includes people from all over the world. The steady growth of IUPHAR and the success of its congresses, begun so modestly in Stockholm over 20 years ago, has given me great personal satisfaction.

To be a retired professor in Sweden has its advantages. The law provides an emeritus professor a laboratory and office space for research and teaching activities, that is, if the available resources allow. I am a very lucky man to have retired from a department with such resources, so I spend my time more or less as before, in my office and in my labs, aided by kind, loyal, and experienced assistants and coworkers. My three hunting dogs accompany me to my office and home as well as hunting, and I can work undisturbed by committee meetings and the other official duties that previously were a heavy burden. I consider myself lucky to have entered pharmacology at the beginning of its rise to an independent discipline and to have witnessed its enormous national and international growth from a branch of physiology to an important discipline in the forefront of medical research. I have never regretted my desertion of physiology for pharmacology.