

The development of non-ionic contrast media

A cooperation between Torsten Almén and Nyegaard & Co.

Amdam RP. Part II, Search for an International Breakthrough. Chapter 9, Breakthrough. In: Amdam RP, Sogner K eds. Wealth of Contrasts Nyegaard & Co - A Norwegian Pharmaceutical Company 1874-1985. Oslo: Ad Noam Gyldendal. 1994:149-155.
(Copied by Ulf Nyman)

Scandinavian radiologists, especially those from Sweden, were among the world's foremost in the 1950s and 1960s. After the war, radiologists from many countries, and particularly from America, flocked to Scandinavia and especially Sweden. Swedish radiologists were extremely active on the international scene; Erik Lindgren and Torgny Greitz are recognized as among the founders of neuroradiology. Perhaps the most famous Swede was Sven-Ivar Seldinger, who developed a catheter technique in 1953. This made it possible to direct the contrast agents directly into a vein, and paved the way for selective angiography - and for Isopaque.

Swedish professors of radiology Olle Olsson and Ulf Rudhe have offered an interesting explanation for the status of radiologists in Sweden. They attribute it in large measure to the efforts of the world's first professor of radiology, Gösta Forsell. From his appointment in 1916, Forsell worked to establish radiology as an independent discipline. In most other countries, including the United States, radiologists were regarded as "assistants" to other physicians. Olle Olsson, through his many assignments in international circles, worked to gain recognition for the Swedish model. By the 1950s and 1960s, Swedish radiology had expanded greatly. Close contact had developed with manufacturers of technical medical equipment such as Elema-Schönander and Svenska Philips. This was the Swedish and Scandinavian environment that Hugo Holtermann sought to exploit.

In 1967 Holtermann initiated contact with Swedish doctors. The communication was two-way, and the prominent pharmacologist Percy Lindgren at the Karolinska Institute was an important supporter of academic-industrial collaboration. In November 1967, Lindgren summarized the significance of cooperation between physicians and Nyegaard & Co:

"One must hope that this developmental work [...] will be a step toward better and less dangerous X-ray contrast media. In accordance with researchers in the field of contrast media, it is also my hope that the increased interest in active research in this area [...] from academic and clinical scientists will continue".

Holtermann kept in touch with three radiologists in particular, Professor Torgny Greitz and two younger radiologists, Erik Boijesen and Sven Paulin. Boijesen and Paulin were invited to spend some time at Nyegaard & Co. Both later became professors, Paulin at Harvard in the USA, and Boijesen at Lund. A fourth Swedish radiologist came to be very important to Nyegaard & Co.: Torsten Almén.

TEAMWORK ACROSS BORDERS

Nyegaard & Co. knew Almén, as he had sought professional cooperation with the company for many years. Almén's doctoral studies in radiology dealt with the effects of X-ray contrast agents, including Isopaque. From 1962-1963 he became increasingly interested in the side effects of injecting established contrast agents into the bloodstream, such as pain, burning sensations and, very rarely, sudden death.

Almén belonged to the active radiology environment in Sweden that was focusing on existing X-ray contrast agents. But his chemically-oriented ideas for developing new contrast agents with fewer side effects were new, and he was ready to put them into practice.

Almén first contacted the major Swedish pharmaceutical company, Pharmacia, but he was not granted a meeting. He chose Pharmacia because it sold an X-ray contrast agent. The logical next step was to contact Nyegaard & Co., which he did through its Swedish representative, Erco Läkemedel. The outcome of his overtures reflects the problems of establishing mutual trust.

The problem was that Erco created a barrier between Nyegaard & Co. and Almén. Erco had represented Nyegaard & Co. since 1951 and it had worked hard on Isopaque sales in Sweden and Denmark. Almén presented his ideas to Erco and its representative, Lars Fondberg, believing that he was thereby communicating with Nyegaard & CO. However, the meeting was not reported to Norway; Nyegaard's information was that *Erco* had started up its own research on contrast agents. In January 1966, Lars Fondberg asked Hugo Holtermann some specific questions about the properties of Isopaque. These questions were especially directed toward the possibility of manufacturing "polymers" of Isopaque, i.e. a chain of metrizoic molecules. Holtermann replied that this was possible, but that he thought a contrast agent of this kind would have a number of drawbacks.

Holtermann understood that such agents would have a lower *osmotic pressure* than traditional contrast agents like Isopaque, and would therefore be less harmful. Osmotic pressure (or osmolality), is a result of particle density (the number of particles per unit volume) in liquids. When particle density is higher in the contrast agent than in the blood,

blood vessels are temporarily damaged in areas containing a high concentration of contrast agent. Linking the contrast agent's molecules would reduce particle density. Ideally, contrast agents should have the same particle density (osmolality) as the human body.

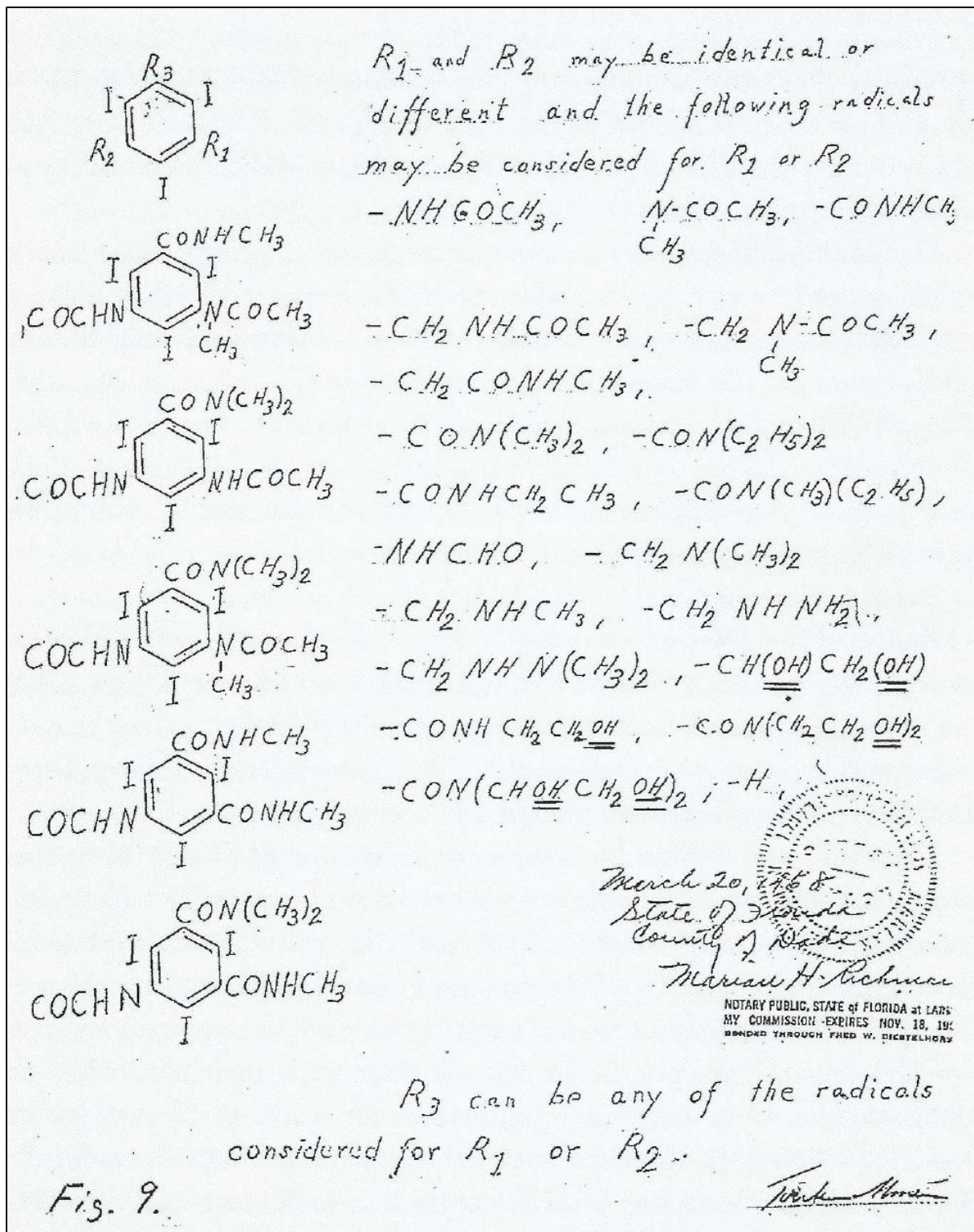
Holtermann was not aware that Erco had heard Torsten Almén's theories; Almén did not know that Nyegaard & Co. was ignorant both of his meeting with Fondberg and his theories. Nyegaard & Co. first became aware of Almén in June 1966, when Holtermann met both Lars Fondberg and Almén at a pharmaceutical convention. Holtermann was surprised that Almén wanted to talk to him. Fondberg, in the meantime, asked Holtermann to avoid discussing polymer contrast agents with Almén, and Holtermann honored Fondberg's request. Therefore, no meaningful contact was established between Holtermann and Almén. Holtermann summarized their first meeting:

"It was my distinct impression that Dr. Almén had not been warned by Fondberg about discussing his ideas with me, and that he in fact would have liked to go into them more thoroughly, and may have been quite surprised when I did not ask more detailed questions".

Contact between Almén and Nyegaard & Co. was thus postponed. Though Erco officially presented itself as a partner of Nyegaard & Co., it kept information from the Norwegian firm. Despite numerous requests, Erco did not give any information about its own attempts to make polymeric contrast agents based on Isopaque. Much time passed before Nyegaard & Co. realized that Torsten Almén also felt that he had been deceived by Erco. But when Ulf Blix contacted Almén personally in September 1967, they quickly realized that they shared the same experience with Erco. Almén expressed his view of the situation forcefully: "In February 1966 I presented to Lars Fondberg the idea of polymerizing the contrast agents by the method described in my doctoral thesis. Since then, the Polypaque project has been surrounded with a great deal of secrecy, even directed at me. Until now I have not received one single written report from Fondberg, or Erco, about Polypaque".

Despite this, Almén had signed an agreement to give his patent rights to Erco as late as spring of 1967 under the impression that Nyegaard & Co. was involved.

Nyegaard & Co. and Almén finally established contact in the fall of 1967, but by then Torstein Almén was skeptical of the entire pharmaceutical industry. He was then living in the USA and had tried to arrange meetings with some of the larger contrast agent companies. He met with Mallinckrodt, but they did not seem particularly interested. His experience with Erco had taught him caution. He was offered a job in Sterling Drug's Biological Division without having presented his ideas. Erco was still the only company with complete knowledge of Almén's theory. In the spring of 1968, he had a portion of his chemical theories notarized in order to be able to prove that they were his own.



After his former experience with the pharmaceutical industry, Torsten Almén exercised caution when he met with the industry. The companies he had approached had either ignored him or tried to take advantage of him. Therefore, he decided to have his ideas notarized by a local sheriff in Florida, USA, where he happened to be at the time.

Nyegaard & Co. took the decisive initiative to establish contact with Almén. Holtermann met Almén in a New York hotel room on February 2, 1968. When Holtermann left New York City, he was convinced that Almén would not work with Nyegaard & CO. A

message then came that Almén wanted to collaborate with a Scandinavian company. This, "as well as the dynamic impression I was given of the contrast agent research at Nyegaard & Co. by Dr. Hugo Holtermann, is the main reason that I did not sign Sterling Drug's proposal".

By May 1968, Torsten Almén was an integrated member of Nyegaard's research team. From this time on, there was continuous cooperation through meetings and correspondence. Nyegaard & Co. had established contact with a radiologist who had ideas for an entirely new generation of contrast agents.

A NON-IONIC X-RAY CONTRAST AGENT

Torsten Almén wanted to create a non-ionic contrast agent. This idea was an integral part of his understanding of contrast agents, but Erco had only partially understood one portion of Almén's project in undertaking its attempt to produce polymeric contrast agents.

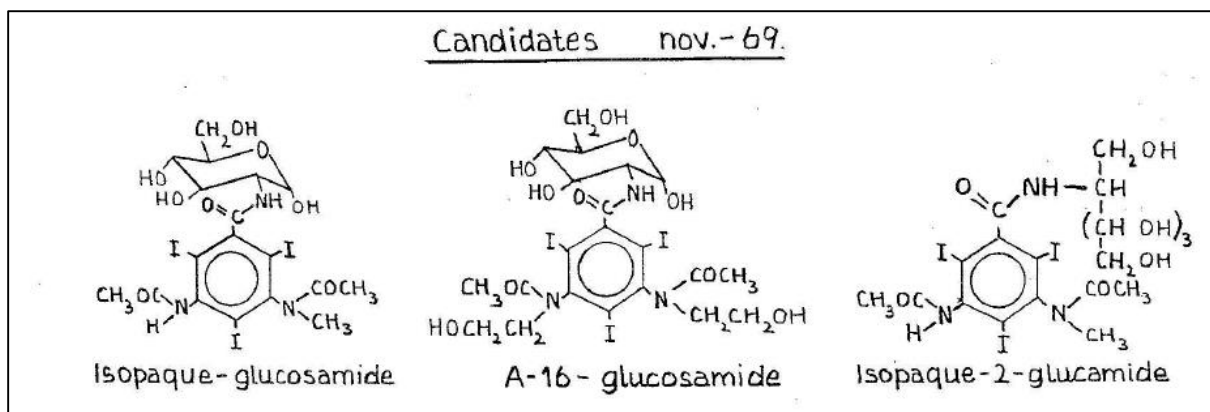
Osmolality was a result of particle density, which was regulated by two factors. The first was the original particle density in the contrast agent solution, and this is what Almén sought to change by linking the iodine molecules together. However, there was a potential problem in that the final solution would be more viscous and therefore more difficult to inject. A finished X-ray contrast agent contains up to about 75 percent of the basic substance in solution.

The second factor influencing particle density was that the density was doubled when the iodinated molecules were dissolved in a contrast fluid. To dissolve the iodinated molecule in water, it is mixed in a base solution. This creates a salt solution, but with twice as many particles as iodinated molecules. The iodinated molecule splits into two particles when electrically charged particles (ions) are formed. Almén suggested making contrast agents which were not salts (non-ionic); these would not split into electrically charged particles and would therefore have lower particle density. By so doing, he hoped to reduce particle density (osmolality) without an undue increase in viscosity.

This conflicted with what chemists thought was possible. They believed that substances containing such a high iodine content had to be salts in order to achieve solubility in high concentrations. Comments Almén received in late April 1969 from a consultant about an article he had submitted to the *Journal of Theoretical Biology* in August 1968 illustrate this:

"The general principle of Dr. Almén's proposal is probably sound. The implementation of it is probably impractical. He seems to be unaware that the ionic nature of the iodinated compounds is an essential property for their solubility in water - so part of his proposal, i.e. using non-ionic hydrophilic compounds, may be invalid".

The research group at Nyegaard & Co. was not really convinced that Almén's proposal could be implemented. Holtermann had little belief in its success, but he was willing to try it. In addition to the idea about non-ionic contrast agents, Almén also presented some fundamental suggestions about how these molecules would have to be constructed in order to be soluble in water. Only one of these suggestions was accepted by Nyegaard's research group: the non-ionic iodinated molecules had to be hydroxyl compounds.



Torsten Almén's idea gave direction to the development of Nyegaard & Co.'s chemical competence. In November 1969 it became clear that Nyegaard's chemists had had success with Almén's idea about non-ionic X-ray contrast agents. The choice was one of three molecules, all of which were based on substances Nyco had synthesized. Before meeting Almén, Nyco had been working on how to reduce side effects, and this was useful in the production of non-ionic contrast agents. The substance which was chosen, "Isopaque glucose amide" (Amipaque), produces fewer side effects because it is non-ionic (Almén's idea), and has lower chemotoxicity. It now had to be dedicated which substance should be developed further.

Nyegaard's researchers had already worked with iodinated substances containing hydroxyl groups, based on observations made by the head of the biological department, Sigbjørn Salvesen. Hydroxyl groups facilitated water solubility, and Salvesen and Nyegaard's research group thought that they also reduced toxicity. This would enable use of contrast agents in the spinal canal and in cerebral fluid. Nyegaard & Co. had been trying to break new ground, but within the framework of ionic contrast agents; when Almén's ideas for non-ionic contrast agents were incorporated into the project, they met with success.

The world's first water-soluble, non-ionic, tri-iodinated substances were developed by researchers at Nyegaard & Co. in November 1968. After only a few months it became clear that many of the other substances were also promising. In terms of reducing

toxicity, this was a giant stride forward. Not only had the researchers reduced osmolality, but their new tri-iodinated molecule also had a lower level of chemotoxicity.

The road that led to this major breakthrough cannot be described briefly. The best way to summarize what happened after the first meeting between Almén and Nyegaard's research staff in June 1968 is perhaps to say that a creative "atmosphere" was established. Almén and the research staff established a supportive professional climate that made it possible to unite Almén's fundamental idea with Nyegaard & Co.'s laboriously developed chemical knowledge.

The success of the non-ionic contrast agents was the result of fortunate teamwork and can be attributed to Nyegaard & Co. as well as Almén. When Almén and Nyegaard & Co. put their heads together in 1968 and 1969, there was a meeting of minds between an individual and a research group. It is a moot point whether one or the other could have developed a non-ionic contrast agent alone. The important fact is that they succeeded together - over 80 different substances were synthesized. In November 1969, after biological and pharmacological testing, Compound 16 (also called "Sweet Sixteen") was declared the best substance.

Less than six months passed between Almén's first meeting with the research group and development of the first non-ionic compound. It took another six months before Compound 16 was produced, and a few additional months of testing before it was chosen as the best non-ionic compound. In an astonishingly short time - from June 1968 to November 1969 - an idea was transformed into a product, which ultimately became known as Amipaque. This startling success must be attributed to the long-term efforts of both sides. Almén, as a physician, had studied the effects of contrast agents on the human body for many years, and with this in mind, he had searched for alternative chemical solutions. His radical ideas probably owed much to his particular starting point. He had a definite goal as regards the properties he wanted in contrast agents, and was not bound by the conventions of chemistry. On the other hand, he was working with what may have been the world's leading chemistry team in this field. Research at Nyegaard & Co. had been achieving good results ever since the 1950s, and its reestablished research team had been constantly working toward new solutions. Some of these were successful, but the same group that so quickly developed a new product in 1969 had also had a number of unsuccessful projects on its record.

A physician and a group of chemists thus managed to develop something of world importance in a short time. Nyegaard & Co. had long been active in the field of contrast agents, and the breakthrough of Amipaque must be seen in this perspective. A reciprocal and

coordinated mutual understanding between the company and the public, and between the company and the medical environment, had been established. The Amipaque breakthrough in 1969 can be interpreted as the fruit of two independent processes: Nyegaard's research within the field of contrast agents, and an extensive medical effort in radiology in the Nordic countries.