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Short Communication

Swedish Model of Developing Innovative Drugs: What Happened and Why?

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Still there are large medical needs that are not met with efficacious drugs. It has for example been an explosion in our understanding of cancer biology but our ability to translate these advances into therapies is poor [1]. To developing new drugs is, however, far from an easy task. It demands scientific competence, theoretically as well as practically, integrity, creativity, engagement, responsibility and, not at least, critical thinking.

Before 1990, the Swedish pharma industry was efficient to discover and develop new drugs that met large medical needs, e.g., terbutaline (Bricanyl), felodipin (Plendil), metoprolol (Seloken) and omeprazol (Losec), together with several others. The research organizations at Draco and Hässle, who developed these best-sellers, were small but with great scientific competence, creativity and innovative capability. Terbutaline was actually discovered before β-adrenoceptors were divided into β1- and β2-receptors, personal communication from my opponent professor Torsten Olsson at my public defense of the PhD thesis. Olsson was central in the terbutaline project. In 1967 Lands reported that there were two types of β-adrenoceptors, β1 and β2 [2]. Terbutaline is a selective β2 agonist. At that time the same person often followed the drug all the way from discovery to marketing. As preclinical member of the iodixanol (Visipaque) team I experienced the same culture in Norway. I started working for Nycomed Imaging in Oslo 1992 and Visipaque was launched 1995. It was really exciting to be a member of the project group during the early marketing period, which among other things included teaching the sales organization of Nycomed Imaging why Visipaque was a better x-ray contrast medium than its forerunners. This was far from an easy task taking in consideration the success with its forerunner iohexol (Omnipaque). Interestingly, Nycomed Imaging still in 1995 worked in accordance to the "Swedish model" (see below), whereas Swedish companies long before had left it and gone into the mega-merger era characterized by a never-ending reorganizations of R&D. In addition the small Swedish companies, and also the Norvegian companies, had a close collaboration with outstanding Swedish and Norwegain researchers, such as the professor of pharmacology Arvid Carlsson (1923-2018; Nobel laureate in physiology or medicine 2000), professor of radiology Torsten Almén (1931 – 2016) (see photo) and professor of nephrology Knut Joakim Berg (1930-2017). When it came to the final formulation of Visipaque, Nycomed Imaging's American collaborator Sterling Winthrop wanted to add "physiological concentration of calcium ions" to it, apparently because it would sound god when promoting Visipaque. Almén together with a few other scientists realized that such a formulation would put patients, particularly during coronary angiography, in real danger because of increased risk of ventricular fibrillation. The Management of Nycomed Imaging was ambivalent for Sterling Winthrop's arguments but not Almén! Later on competitors argue but without any proof that Visipaque was more nephrotoxic than its forerunners. Knut Joakim Berg on the other hand was convinced from his clinical experience with Visipaque that it was less nephrotoxic. This was a critical issue for Visipaque and Nycomed Imaging once again was ambivalent but Berg managed to convince them to conduct a study. This study published in New England Journal of Medicine [3] showed exactly what Berg had predicted, i.e., Visipaque was less nephrotoxic than its forerunners. As a result the sale of Visipaque increased tremendously.

However, very soon after the launch of Visipaque the President of Hafslund Nycomed (the mother company of Nycomed Imaging) Svein Aaser announced in an extra issue of the internal journal of Hafslund and Nycomed, AGENDA, that Nycomed Imaging was going to merge with the American IVAX Coperation (see front page of Agenda). This was apparently a company nobody had heart about and a majority of owners stopped the merger. However, two years later Nycomed Imaging merged with Amersham, at a 55%/45% bases. At that time Nycomed Imaging had at least three big products (Omnipaque, Omniscan and Visipaque), whereas Amersham only had one (Myoview). Nevertheless, this started an era of molecular imaging with a strategy of putting radioactive technetium on receptor selective antagonists in order of image pathological upregulation of, e.g., membrane angiotensin II receptors of the heart. Every receptor pharmacologist should realize that this is a mission impossible, due to a very low concentration of membrane receptors. On the other hand membrane receptors are ideal target for therapy, e.g., subtypes of β-adrenoceptors and angiotensin II-receptors in cardiovascular diseases. The company was then bought up by GE 2004 and became GE Healthcare. In the coming years, more or less all research activities moved away from Norway.

Front page of the internal journal of Hafslund Nycomed, AGENDA, where President Stein Aaser announces the merger (fusjon in Norvegian) with IVAX Corperation.

During the last 30 years, or so, scientifically driven R&D organizations have gradually been replaced with business and development (B&D)-driven organizations in the pharma industry, where the question about profit has become increasingly important throughout the whole chain of drug development [5,6]. However, the profit as the B&D-define it is rather different from the pharma industry view in the mid-20th century, when George W Merck, the president of Merck and Co., noted that "We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been" (Merck, 1950) [6].

Critical scientists in B&D-driven organizations have either to leave the company or fully adapt to the B&D's way of "developing" innovative drugs. Criticism from scientists against the B&D's way of working is typically seen upon as disloyalty from the Management. This is of course strange in an activity that describes itself as a knowledge-based one. A situation probably best explained by inherent conformity, as described by the Asch paradigm [7]. The main body of knowledge in creative/innovative-based industry is expected to be found among its scientists and not in the Management. Nevertheless, that has resulted in B&D-driven R&D organizations that spend an increasing amount of time to figure out for how many billions of dollars a fancy drug is going to sell for, and thereafter try to create that particular drug. In other words it has become increasingly important to "count the chickens before they are hatched". PowerPoint slides, rather than peer-reviewed publications, have been increasingly important [6]. Few of them in the B&D-driven pharma are able to write scientific articles, and hence few are able to read scientific articles and draw appropriate conclusions in the company's field of interest. Every complicated matter is simplified in a way that makes the Board and Management to believe they understand the problem. Consequently, the inverse relationship between invested money and productivity in the pharmaceutical industry has for many years been a reoccurring theme. For Big Pharma, finding new blockbuster drugs is becoming increasingly challenging and expensive, and consequently extremely more expensive for the society. Interestingly, since 2013, smaller enterprises have increased innovation and delivery, bringing a disproportionate amount of new products to the market (https://www.pharmalive.com/annual-report-2019-top-10-pipelines-to-watch/) and bringing new hope for the future. However, of all thousands of Bio/Medtech companies founded, the great-great majority has failed in terms of finding viable clinical drug candidates and/or in generating the necessary revenues to survive. This, however, has not prevented investors, founders, and company employees from becoming wealthy, regardless of the companies' fates and/or their science [6], or as Mark Knopfler express it, "money for nothing".

An absolute prerequisite for an R&D organization to develop new drugs is a high degree of creative/innovative capacity. Conformity is probably the most dangerous enemy to innovation and creativity. Creativity is something that evolves spontaneously and there is no manual on how to build a creative organization. B&D-driven guys seem to believe they can create creativity and innovation by holding training courses on the subject, where they appoint "champions" to inspire others in the organization to be more creative and innovative. My own experience is that this particular approach has the opposite effects, i.e., it destroys creative and innovative capacity among scientists that still have it. To increase scientific competence in the B&D-driven organization, scientific advisory boards, are appointed. These Boards typically consist of payed external experts. However, in opposite to Arvid Carlsson and Torsten Almen, and Knut Joakim Berg, these external experts rather typically consist of yes-men. The aim here seems explicitly to legitimize the ideas of the B&D-driven guys, particularly when it comes to interactions with responsible authorities. This has resulted in a situation where the pharma industry has lost most of its pharmacological/physiological competence that is needed to succeed in developing new drugs in the real world.

Market analyzes of how much a fancy drug is going to sell for are afflicted with great uncertainty. This and ongoing blockbuster hysteria are most probably involved in today's disproportionate low productivity of innovative drugs in Big Pharma [5,6].

Another apparent cause to low productivity is the B&D-driven guys fascination of the molecular biology's turn on the computer - turn off the brain [6] discipline, where X gives Y, which in turn gives Z. This is of course an attractive model for guys with a limited knowledge in physiology and pharmacology. Today's shortcomings in preclinical competence apparently result from a change in the

culture of biomedical science, from a physiological/pharmacological to a molecular biology culture. Molecular biology is a discipline lacking a quantitative approach and that has contributed to a lack of biomedical scientists trained in pharmacology [6]. Key decisions in the world of molecular biology is often made from "statistics-free" effects of a single dose of a compound and evaluated at a single time point using a transfected target or transgenic animal. Consequently the basic premise of pharmacology is negated and the Law of Mass Action is replaced with "all-or-none" responses.

Another serious problem in the era of molecular biology is the uncritically use of nude mice in experimental cancer research. A collection of mouse cancers respond to chemotherapy more efficiently when they are implanted in syngenic immune-competent mice as opposed to immune deficient hosts, i.e., nude mice [see 8]. The immense importance of the immune system for the outcome of cancer treatment is not a new idea but has for many years severely suffered from the uncritically use of immune deficient mice. Today, immune therapy is probably the hottest area within cancer treatment.

The pharmacologist Sir James Black (1924-2010) received the Nobel Prize in physiology or medicine1988, especially for his outstanding discoveries regarding pharmacological treatment of hypertension, discoveries that have had a tremendously impact on mortality in heart diseases. More than 25 years ago, Black and colleagues put up a warning flag for oversimplifications in molecular biology in the book "The Logic of Life: Challenge of Integrative Physiology" [9]. This problem was, according to him and his co-authors, caused by a paradigm shift from a physiological/pharmacological one to a typical genetic sequential paradigm. According to the genetic sequential paradigm, creating a new drug is about identifying the right target and the silver bullet, and "We are told over and over 'once we know the structure of the gene product, then new drugs will follow…'"[9]. However, according to the physiological/pharmacological paradigm, life is much more complicated, where a multitude of signals are going on in parallel, creating non-linear systems. As an example, on May 3, 1998, New York Times announced on the front page that Judah Folkman had discovered two natural compounds, angiostatin and endostatin, that dramatically shrunk tumors in mice by cutting the cancers blood supply. Along the story was a quote from Nobel laureate James Watson: "Judah is going to cure cancer in two years". Methods from what we today know as molecular biology are fantastic tools but the results have always to be put in a physiological/pharmacological context, in order to avoid false conclusions and hopes among cancer patients.

After B&D-driven guys have identified a fancy drug, it looks like every scientific principle is set aside and replaced with a "religious" conviction throughout the entire organization that this particular drug for sure will meet the medical need and sell for billions of dollars, according to their market analyzes. The extremely low frequency of successes in the real world makes every effort to evaluate the soundness of the market analyses impossible. Their favorite explanation of the recurrent failures seems to be problems with FDA and other responsible authorities [5,6]. Furthermore, the total cost of development is proportional to the number of failures and the demand of better earning is rising among investors, and the B&D-driven guys are forced to come up with even more optimistic estimates and fancy PowerPoint presentations. The most plausible explanation to the recurrent failures in developing new innovative drugs in the pharma industry is weak physiological/pharmacological steering in their drug development projects (see above).

Sweden's biggest drug success, omepralzole (Losec) [4], is an interesting example. Omeprazole was developed at the interface between an older era governed by physiological/pharmacological competence and a newer era governed by a growing number of B&D-driven guys and molecular biologists. Hässle in Gothenburg succeeded despite a strong resistance from its mother company Astra to get omeprazol approved for marketing 1988. During 1970's Hässle collaborated with Abbott in the development of what later became omeprazol. However, Abbott's market analysts at that time concluded that such a product would have a very limited annual sale of just a few million US dollars [4]. The collaboration between the companies was broken, and Hässle was forced to ask for governmental money in order to take omeprazol into clinical phase.

In the 1990' I had the great opportunity to work together with professor Torsten Almén (see photo) in connection with the development of the x-ray contrast media, iodixanol (Visipaque). As a young radiologist during the 1960', Almén experienced that the x-ray contrast media caused an intense pain after administration. The use of these contrast media was also restricted by a high degree of toxicity [10].Rather soon Almén figured out how to solve the problem. After the Swedish company Pharmacia had turned down Almén's idea, he approached the small Norwegian pharmaceutical company Nyegaard and Co. For making a long story short, the head of research at the company, Dr Hugo Holtermann (1916-2003), believed in Almen's idea, and after a relatively short period of time Nyegaard and Co marketed the first of Almen's x-ray contrast agent, metrizamide (Amipaque) 1978. Amipaque was followed by an improved version, iohexol (Omnipaque) 1982. A success that made Nycomed Imaging AS (former Nyegaard and CO) becoming the world leading producer of x-ray contrast media [10] - an industrial adventure without comparison on the Norwegian mainland. However, Almén did not rest on the laurels but saw further pos-

Torsten Almén during launching of Visipaque 1995 in Vienna. Photo Jan Olof G Karlsson

sibilities to improvement that resulted in iodixanol (Vispaque®), which was launched 1995. Almén's discoveries caused a revolution within the field of medical imaging, something that over 100,000 patients benefit from every day.

If you analyze Almén and Holtermann's success a little bit closer, it is obvious that Holtermann understood Almén's brilliant ideas as soon as he heard about them, although he to begin with was a little bit pessimistic if they should succeed in synthetizing x-ray contrast media in line with Almén's ideas. Holtermann's scientific perception and integrity was of course an absolute prerequisite for the success. An R&D organization headed by opportune B&D-driven guys would surely not have understood Almén. Hugo Holtermann with a PhD in chemistry from Oxford was, like Torsten Almén, definitely not a yes-man.

Today there is almost nothing left of the Swedish and Norwegian pharmaceutical industry. After omeprazole, launced 1988, the Swedish industrial research organizations have failed to develop new innovative drugs, and consequently, most of the industrial research activity has been shut down. According to my view, this has happen as a consequence of a gradually replacement of science-driven R&D in exchange to a B&D-driven R&D, during more than 30 years. The majority of those who used to work within the pharma R&D departments have lost their jobs. Today you find many of them in Bio/Medtech starts-up in Sweden and Norway (and the rest of the world), either as employees or as consultants. It seems to be high expectation among Swedish politicians and investors that these starts-up should bring Sweden back to its top position among pharma companies. However, I ask myself if ex-employees from B&D-driven pharma companies are the moat suited for the task, where a master's in business administration (MBA) seems to be immensely more important than scientific vision. Although many of these B&D-driven guys have a PhD, almost all of them lack experience from independent research. I am convinced that Bio/Medtech start-ups need trained and critical minded physiologists and pharmacologists to achieve the goal, i.e., to find the right drug candidates, develop them and achieve marketing authorization.

Unfortunately, in the world of molecular biology there are very few trained physiologists and pharmacologists to find. However, pharmacology and physiology are still important subjects in biomedical higher education, not at least in the education of physicians. So there are still possibilities to educate forthcoming candidates and fix the problem. Going back to the old way of developing innovative drugs, i.e., based on a physiological/pharmacological paradigm, would furthermore make drugs considerably less costly and would also give developing countries a great chance to enter the scene of drug discovery, preclinical and clinical development and marketing.

Conflict of interest

The publishing fee ($299) was paid by Karlsson-Tuner Invest AS, I Norwegian company mainly owned by the author.

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