

New approaches to gynecological therapies for chronic women's diseases

Hope of **rapid pain relief**

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Gynecology



The birth control pill has been synonymous with reliable hormonal contraception for nearly fifty years now. The inventors of this once revolutionary idea have long since set their sights on new goals: researchers at Bayer HealthCare are working on new active ingredients for the treatment of painful gynecological disorders such as fibroids and endometriosis.

Women might talk about the problem amongst themselves, but men usually know little about it. After all, this long trivialized disease only affects women. We are talking about endometriosis, a chronic and often highly painful disease in which tissue very similar to the mucous membrane lining the uterus settles in areas outside of the female sex organs. The primary symptoms of endometriosis are diffuse lower abdominal and back pain as well as painful menstrual periods. This not only severely impairs a woman's sense of physical well-being, it can also cause psychological problems and create a significant burden on a partnership as it is widely considered to be the most common reason for inability to conceive.

Regulated by female sex hormones, the uterine mucosa (also known as the endometrium) builds up in monthly cycles during a woman's potential child-bearing years, which begin with her first menstrual period as a young teenager and end decades later with menopause. Only when the required thickness has been reached can a fertilized egg cell comfortably embed itself in this tissue for nine months. If fertilization does not take place, most of the mucous membrane breaks down again and is flushed out of the body with the menstrual blood.

"Yet in approximately ten percent of women – some estimates are even higher – small pieces of the endometrium travel to areas of the body where they don't belong and start growing there," explains Professor Ursula-Friede-

rike Habenicht, Head of Therapeutic Research in Bayer Schering Pharma's Women's Healthcare Business Unit. This might be on the edge of the pelvis, bladder, intestines or ovaries. How they reach these locations is a mystery. Most experts believe that this occurs during menstruation when individual mucous membrane cells travel backwards to the fallopian tubes and from there into the abdominal cavity. Yet this would not explain why misplaced tissue has, in rare cases, even been found in the lungs. According to another theory, uterine cells may end up in the wrong places as a result of transport through lymphatic and blood vessels.

Chronic pain from renegade mucous membrane

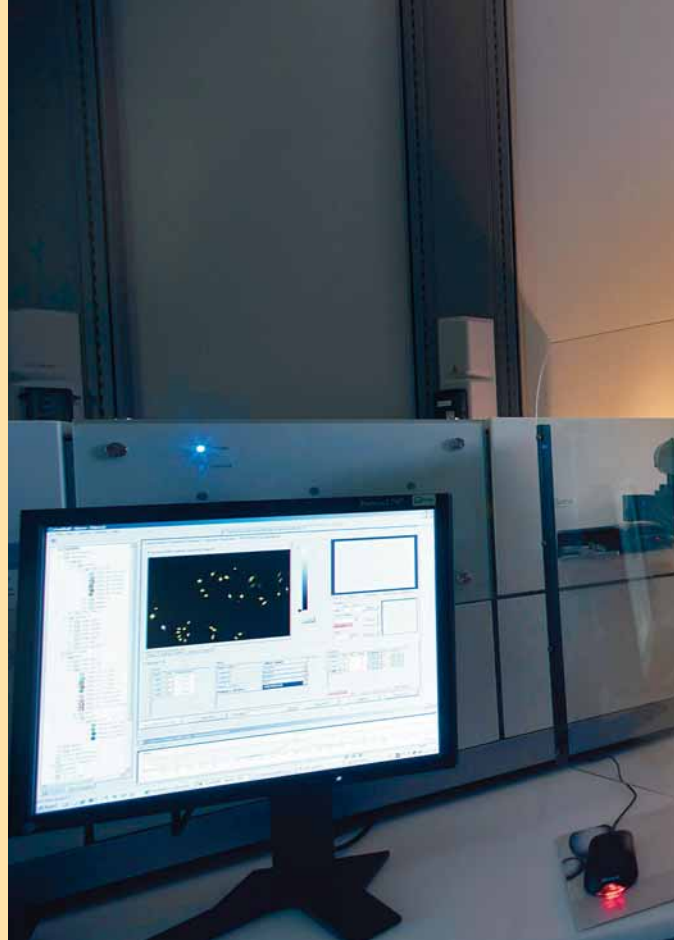
What is undisputed, however, is that the lost uterine mucosa responds to hormonal changes in the female cycle just as though it were still in the uterus, thus growing during the course of the cycle. Some women don't notice this process, but many patients experience chronic pain in the lower abdomen that may occur independently of their monthly period.

At first, the symptoms are non-specific and discounted as normal menstrual complaints. In many cases, endometriosis is not discovered until those afflicted consult a gynecologist about their inability to become pregnant. The disease can only be diagnosed with certainty by means of a surgical procedure known as laparoscopy, during which the diseased area is usually

Painful periods: Endometriosis affects many women, with an estimated 11 million sufferers in the European Union alone.

The pill from Berlin

Germany has a long tradition of hormone research. In 1928, Progynon®, the first hormonal drug for treatment of menopause complaints, was introduced to market. In 1938, the chemists Walter Hohlweg and Hans Inhoffen were able to synthesize ethinylestradiol, which is still used in the pill today. The progestin progesterone was harvested from the ovaries of pigs and introduced in Proluton® in 1933. A year later, Schering researcher Adolf Butenandt discovered how to produce the substance synthetically. The necessary groundwork was thus laid for the development of hormonal contraceptives. Further research was hampered by the National Socialist party which had then come to power. In the 1950s, the American Gregory Pincus picked up on the work performed in Germany. The first birth control pill, Enovid®, was introduced to market in the United States in 1957 for treatment of gynecological disorders. Scientists in Berlin were meanwhile working on a product of their own. In 1961, the little green pill Anovlar® became available in pharmacies. Schering continued to strengthen its pioneering role with many innovative products. Birth control pills with the unique progestin drospirenone offer an additional medical benefit. Today, Bayer Schering Pharma is the world market leader in the field of hormonal contraception.



In search of active ingredients: with the help of high-throughput screening, Janine Schmalowsky is searching for new substances as effective medications for women's diseases.

removed or sclerosed. Unfortunately, the relapse rate is high: three out of four patients experience symptoms again within five years.

Hormone experts are researching the causes of endometriosis

There is thus still substantial need for research in order to develop new forms of therapy. This work must be based on a comprehensive understanding of the female hormonal cycle, an area in which the Bayer Schering Pharma researchers are experts. After all, the company has been studying sexual hormones for nearly 100 years now and is considered a pioneer in many areas. In 1928, Schering brought the first hormonal product to market and would later become inseparably linked with the birth control pill following the introduction of Anovlar® to the European market in 1961 (see box "The pill from Berlin").

Now Habenicht's team of researchers is seeking to leverage their experience in the treatment of endometriosis as well. "Thanks to molecular medicine, we now have methods at our disposal which did not exist ten years ago," says the hormone researcher. "For example, we can now use genetic analyses to determine exactly how the uterus of an endometriosis patient differs from that of a healthy woman." Evidence is mounting that, in addition to hormones, two other factors play a critical role in the development of the disease: firstly, the formation of blood vessels, a process also known as angiogenesis that is required for endometriosis to grow. Secondly, inflammatory processes could promote endometriosis: it has long been known that endometriosis patients carry certain inflammation markers in their blood. Scientists previously believed that this was the result of endometriosis and not part of the cause, but more recent

findings indicate that inflammation may lay the groundwork for this painful women's disease. "We are currently researching in three areas: anti-hormonal approaches, anti-angiogenesis and in the field of anti-inflammatory agents," says Habenicht, explaining the strategy pursued by Bayer Schering Pharma.

This research has already yielded initial success: a medication developed by the experts in Berlin containing the active ingredient dienogest – a synthetically manufactured progestin – could be the first low-side-effect oral drug approved specifically for long-term treatment of endometriosis. Clinical testing has been successfully completed and the product is scheduled to be submitted to the regulatory authorities in the near future.

Using an antagonist of progestin, an anti-progestin, Habenicht's research team is also seeking to attack another



Hormone expert: Professor Ursula-Friederike Habenicht (right) has spent many years researching the processes that occur during the female cycle. In addition to contraception and menopause management, she and her team are now seeking to develop new therapies to combat gynecological diseases.



women's disease: fibroids, the most common gynecological disorder among women of child-bearing age. More than 20 percent of all women aged above 35 suffer from these benign uterine tumors that occur mainly in the muscle layer of the uterus (myometrium). Fibroids can even lead to infertility or to complications if pregnancy does prove possible. The main form of therapy for fibroids is still an extremely radical one – complete removal of the uterus in a procedure referred to as hysterectomy. Approximately 600,000 hysterectomies are performed in the United States alone each year, approximately one-third of them due exclusively to fibroids.

Research on new types of therapy for fibroids

"At the same time, many women go untreated because they accept the pain and don't go to the doctor, as a result of

which the tumors are never diagnosed," explains Habenicht. In her experience, she has also found that some experts prefer to remove the uterus in order to eliminate all problems. She therefore hopes that increased research and the successful medicinal therapies it yields will help change these attitudes as well.

Both endometriosis and fibroids are diseases affecting younger women. Because they are dependent on hormones, these disorders disappear entirely of their own accord during menopause once the uterus has permanently stopped functioning after the last menstrual period. That is no consolation to women afflicted by one of these diseases in their mid-thirties, however. In addition to contraception and menopause management, Bayer Schering Pharma will in the future create a third strong pillar of business by orienting its research to forms of therapy for gynecological disorders.

www.endometriosis.org



This website contains a global forum for information about endometriosis.