

Gynecological therapies for chronic women's diseases

# When **pain** becomes **the rule**



*Extremely heavy menstrual periods and diseases such as endometriosis or uterine fibroids can cause intolerable pain in some women. What's more, they can also be the reason for a woman's inability to conceive. Researchers at Bayer HealthCare are now working on novel treatments for these conditions. They have already developed an effective medication for the treatment of endometriosis – and more are to follow soon.*

Every four weeks, some women have a very hard time. They make sure these days are clearly marked in their diaries: this is not the time for going out with friends or for business trips. For these women, these are the monthly days of misery – with heavy menstrual bleeding sometimes lasting more than a week, or recurrent pain with more or less severe discomfort in the lower abdomen. "Of course these are not life-threatening conditions. But days like this when a woman has to change her tampon every hour have a severely negative impact on her daily life," says Professor Ursula-Friederike Habenicht, Head of the TRG Women's Healthcare at Bayer HealthCare in Berlin. And heavy blood loss has other consequences, too. If a woman loses too many of her red blood cells and thus

too much iron during her monthly cycle, she will have to regularly take iron supplements.

### **Tissue from the uterus becomes sidetracked in the body**

The severity of menstrual symptoms varies from month to month and from woman to woman. But recent studies in the United States show that the number of working days lost as a result of menstrual complaints is considerable. For about one woman in ten, the pain before and during a period is sometimes intolerably severe because these women suffer from a disorder known as endometriosis. Pain during sexual intercourse and diffuse lower abdominal pain can also be symptoms of this condition.

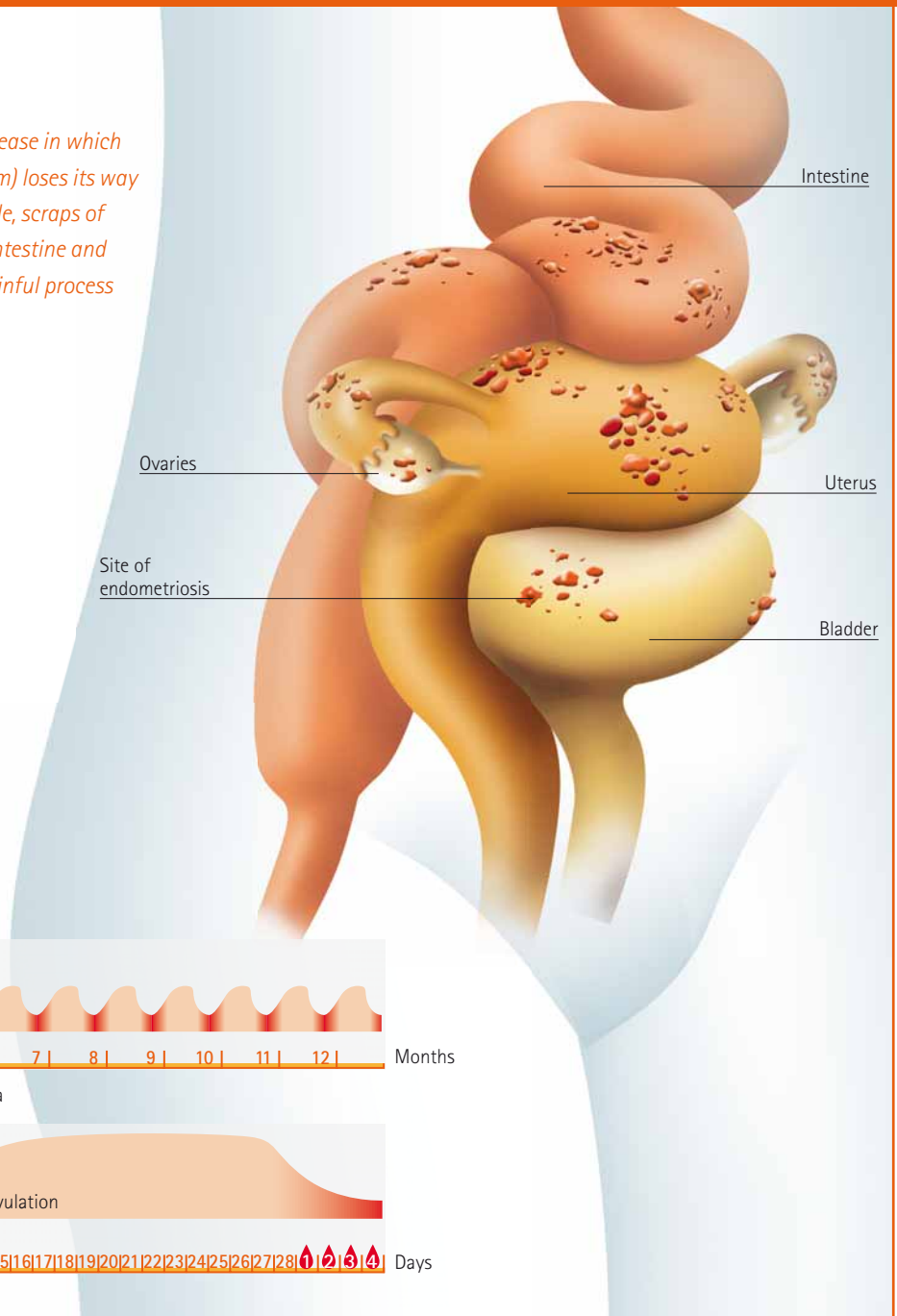
One of the possible causes of endometriosis lies in the menstrual cycle itself and is termed retrograde menstruation. This means that some of the menstrual blood and small scraps of tissue from the discarded uterine lining travel backwards through the fallopian tubes into the abdominal cavity. According to Habenicht this probably happens to every woman at some time in her life. But the situation where the uterine tissue actually attaches itself to such unusual sites as the abdominal lining, fallopian tubes, ovaries, bladder or intestine, growing in response to the female cycle and leading to inflammatory changes, only occurs in 5 to 10 percent of women. "What allows the tissue to become established outside the womb at all remains a mystery to us,"

Relieving women's pain: menstruation can sometime cause unbearable pain (photo, left). In Bayer HealthCare's laboratories, Lam Cam Quoc (photo, right) examines ovum-cumulus complexes that as helper cells support ovulation.



## Lost in the cycle

Endometriosis is a benign, chronic disease in which mucosa from the uterus (endometrium) loses its way in the body. During the menstrual cycle, scraps of tissue can migrate to the bladder or intestine and start growing there - an extremely painful process for affected women.



says Habenicht. "It also often turns out that endometriosis is the reason why a woman is unable to conceive," explains Dr. Thomas Faustmann, a gynecologist in Bayer HealthCare's Global Medical Affairs department. "If the disease is not treated, it progresses and can lead to scarring and adhesions, in some cases to the ovaries and the fallopian tubes as well,

and can make it difficult or impossible for the woman to become pregnant."

For a long time there was no satisfactory treatment for endometriosis. But like the uterine lining itself, the endometriotic lesions are controlled by the hormonal cycle. This was the starting point taken by the scientists at Bayer HealthCare in their search for therapeutic solutions. They developed

a treatment which can be used for a longer duration than was possible with existing therapies and is designed to have as few side effects as possible. The tablets containing two milligrams of the synthetic hormone dienogest - a progestogen - suppress ovulation and keep women's estrogen levels low. The result is less stimulation of the uterine lining and the misplaced uter-



Pain-free days: menstrual blood or uterine tissue probably migrates to the abdominal cavity in all women for reasons that are not yet precisely known to medicine. A team headed by Professor Ursula-Friederike Habenicht (photo, above), Head of the Therapeutic Research Group Women's Healthcare at Bayer HealthCare, has come up with new initial approaches which are currently in the clinical phase.

ine tissue. The pain that occurs when the outermost layer of the uterine lining is shed is also less severe.

### Combined therapeutic approach to relieve pain

Bayer's researchers are also using genetic analyses in their exploration of further avenues of treatment. For example, with the help of special gene chips they have found that the cells of the intact uterine lining in women with endometriosis differ from those in healthy women. Some DNA segments are more active than others. New treatments or products could regulate this over-activity of the genes appropriately. Up to now, research has concentrated mainly on hormonal aspects. "But as these treatments always also interfere in the female cycle, we are devoting more attention to other treatment approaches too," explains Habenicht. After all, hormones are not the only point of attack in endometriosis. Because the disease is associated with an increased inflam-

matory reaction, counterregulation of the overactive immune cells is another potential approach. Bayer's researchers are also working on tackling the pain at its roots. "We now know that new nerves grow specifically into the endometriotic lesions," says Habenicht. This explains the severe pain.

It usually takes up to three years before a woman suffering from this problem goes to the doctor for the first time. Another eight years pass on average before the diagnosis of endometriosis is made. In 55 percent of women who are unable to become pregnant, for example, the condition is only diagnosed in the course of the investigations to establish the possible causes of the inability to conceive. The condition mainly affects women aged between 25 and 40, but teenagers can also suffer from endometriosis. "Therefore what we particularly need is an easier way to diagnose the condition," says Dr. Ulrike Fuhrmann, a biologist and Head of the Department of Gynecological Therapy I in Women's Healthcare Research. Currently there

## Interview



### "A major research gap"

Ludwig Wildt is Professor at the Department of Gynecological Endocrinology and Reproductive Medicine at the Innsbruck School of Medicine. *research* asked him some questions on the topic of women's health.

#### Why is there a need for a separate discipline of women's health at all?

The female cycle means that some diseases present differently in women or are subject to cyclic changes. This applies just as much to epilepsy and autoimmune diseases as it does to headaches. We also know, for example, that cardiovascular diseases are often underdiagnosed in women simply because the symptoms are different. We need to raise awareness of this among our doctors.

#### Why has the issue been neglected so far?

The problem is that many studies have so far only been conducted in men. Women and children were often not included. And then cycle-related changes were often attributed to the women's mental condition and less to actual changes in their bodies.

#### In which area is particularly intensive research needed?

So far research has concentrated on malignant diseases such as breast cancer and cervical cancer. But in future we need to find out more about the influence of sex hormones on the immune system and the body as a whole. At the moment there is still a major research gap here. We need a better understanding of diseases such as endometriosis and fibroids, because once a disease has been fully understood, new, particularly promising treatments become possible. It's only then that we can develop a suitable drug.



Research for women's health: biologist Dr. Ulrike Fuhrmann and gynecologist Dr. Thomas Faustmann (left photo, left to right) were part of the team that developed a therapy for endometriosis. During the course of their work, Bayer HealthCare's scientists tested the efficacy of numerous substances (photo, right).

is neither a blood test nor a comparatively simple and reliable diagnostic procedure available.

The scientists in Habenicht's team are therefore also working intensively on a diagnostic test with special markers which could help gynecologists to identify the disease with tissue sampling. The only diagnostic procedure available at present is laparoscopy under general anesthetic to identify and surgically remove the misplaced tissue. "However, we're not sure that the surgery itself doesn't also stimulate new lesions," reports Habenicht on the current research debate. Indeed, about 30 percent of the patients develop symptoms again within five years. This means that afflicted women sometimes have to undergo surgery two to three times. "We hope that with medication we will be able to spare some of these women such massive interventions in future," said Habenicht. Recent investigations show that not only patients but also doctors prefer medication to a surgical intervention.

This also applies to another disease to which the Bayer researchers are currently devoting a lot of attention: growths in the muscle layer of the womb known as fibroids, whose cells divide more often than they should for currently unknown reasons.

### **Fibroids: more than 35 percent of women are affected**

More than 35 percent of women have a fibroid in the womb. Although the tumors are benign they can become so large that they press on the bladder or cause profuse bleeding. The growth, which can become as large as a baby's head, must then be carefully removed from the womb in a lengthy operation. Or, in women who do not wish to become pregnant, the doctors remove the tumors together with the entire uterus. "An operation like this is a huge burden for the patients," says Habenicht. Doctors only refer their patients to a surgeon if there is no other option. If a fibroid is not excessively large or grows very slowly,

bleeding can be controlled with medication. Drugs that artificially lower the levels of sex hormones in the blood known as GnRH analogues can also reduce the symptoms: they reduce hormone production by the ovaries and cause the fibroids to shrink. But hormone deprivation can have severe side effects such as hot flashes and bone loss, similar to the changes that occur with menopause. This means that GnRH analogues as monotherapy can only be prescribed for a limited period of time. As the growth of the fibroids depends particularly on the progestogen level, the researchers at Bayer HealthCare are currently testing an anti-progestogen in clinical studies.

### **Search for new active ingredients: links to cardiology**

In order to interfere as little as possible in the menstrual cycle, scientists are looking into different substances. Habenicht's team is getting support from their colleagues in cancer research, amongst others. There is also



Systematic search for active ingredients: using bioanalytical methods, scientists from Bayer HealthCare in Berlin investigate how pharmaceutical substances can be used to improve the regulation of the hormonal balance and thus help relieve the symptoms of endometriosis or fibroids.

intensive collaboration with the company's heart specialists. Says Habenicht, "When we realized that the matrix of the fibroid, in other words its basic framework, is also considerably altered we looked to see where we could find comparable phenomena." Their search was successful. There are also fibrous and disorganized – fibrotic – changes in heart tissue similar to those in the uterus.

Numerous cooperations with external scientists also contribute to the birth of new ideas: the researchers at Bayer HealthCare are constantly expanding their network with experts from universities and hospitals in Germany, Europe, the United States and China. In future, for example, they want to focus more attention on the tissue in the uterus. "The tendency so far has been to look at the cell layer responsible for endometriosis separately from the areas of tissue where the fibroids grow," says Habenicht. Up to now practically no attention has been given to the interaction between the two adjacent cell layers. "This is an

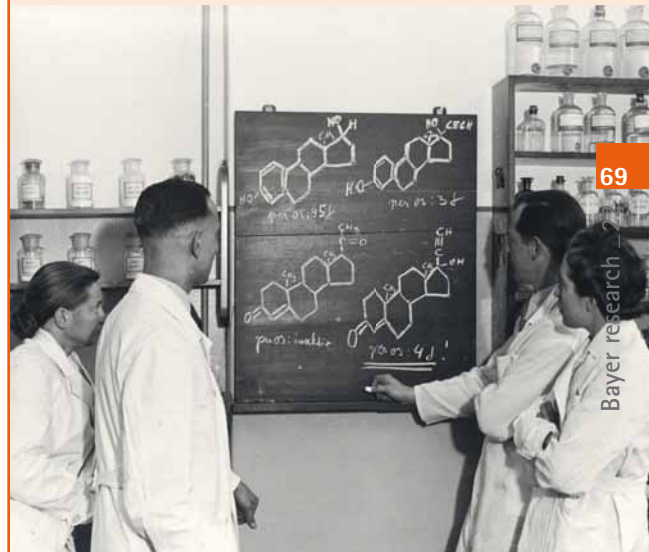
idea we want to pursue more intensively in future. We want to learn more about the communication between the cells in the uterus," she adds. After all, fibroids and endometriosis are just two reasons why some women have heavier menstrual periods or pain that recurs every four weeks and interferes with their daily lives.



[www.research.bayer.com/gynecology](http://www.research.bayer.com/gynecology)

Links to information and literature on this topic

## More self-determination: 50 years of the Pill



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*It is half a century since the contraceptive pill was first introduced to the market. Its launch was a milestone in medicine and meant liberation for many women. The Pill has fundamentally changed society. When the Berlin-based company Schering, now part of Bayer HealthCare, launched Anovlar® in Germany in 1961, only a few selected gynecologists initially knew about the new product that was then available in pharmacies. This is because the little green pills were initially not licensed as a contraceptive but for the treatment of menstrual symptoms.*

*Today about 34 million women in the industrialized countries use oral contraceptives from Bayer HealthCare. But the pill also improves the situation of women in developing countries. Every year, 76 million women have unplanned pregnancies and more than 500,000 die of complications during pregnancy or childbirth. What's more, every unwanted child increases the risk of poverty for their families. Fifty years ago, thanks to the pill, women were able to plan their lives themselves for the first time.*