Growing up on a farm reduces the risk of asthma and allergies. Allergy specialist Erika von Mutius is studying why this is so, as the answer could suggest new ways of preventing such disorders.

At the outset, Erika von Mutius dispels the notion that asthma and allergies are unpleasant but basically tolerable illnesses. As a pediatrician, von Mutius knows all too well that this is untrue. Children who develop these disorders “are really sick”, she says. Moreover, such ailments, which arise when the immune system fails to distinguish correctly between harmless and pathogenic agents, are a major public health problem and their incidence continues to rise. According to the Robert Koch Institute, some 17% of children in Germany suffer from bronchial asthma, neurodermitis, hay fever or food allergies. In the years 1994/95, it is estimated that one in ten children displayed symptoms of asthma; 20 years later, this figure had increased by 30%. The data for hay fever and allergic skin disease show a similar trend. Strikingly, two centuries ago, hay fever was practically unknown.

“A little dirt / does not hurt”

Those are but dry statistics. But, as Chief of the Outpatient Clinic for Asthma and Allergies at Dr. von Hauner’s Children’s Hospital, which is part of Munich University Medical Center, Erika von Mutius is motivated by what she experiences on the wards. In her work as a physician, and as Professor of Pediatric Allergology at LMU, her primary aim is to find ways of helping sick children to cope with their condition, which often lasts a lifetime. For years she has been following up a lead – the so-called “farm effect” – which she hopes will guide her to that goal. The term refers to the observation that children reared on farms have a far lower risk of developing allergic disorders than city kids do. The so-called “hygiene hypothesis” explains this by postulating a link between exposure to a diverse population of microorganisms and reduced risk of autoimmune disease. As the saying goes, “a little dirt / does not hurt”.

In interviews, von Mutius says she is fascinated by the idea that aspects of one’s upbringing can protect one against asthma and other allergic conditions. Understanding the basis for this effect would allow us to apply it to children who have not been exposed to such an environment. Seen in this light, “our findings have an enormous preventive potential”, she says. Indeed, the German Research Foundation (DFG) has recognized the broad implications of her work by awarding a Leibniz Prize to her. The generously endowed accolade is conferred on only about a dozen recipients each year, and is regarded as the most prestigious German award for research. Erika von Mutius became interested in the farm effect about 15 years ago, when she was looking for possible connections between air pollution and the prevalence of croup and allergies. She and her group, as well as workers in other laboratories, subsequently discovered that children brought up on farms are less likely to display symptoms of allergy than their playmates in the same village or children who live in towns. Indeed, the risk of developing asthma in an urban setting is twice as high. For hay fever, the effect is even more obvious; young city dwellers are three times more likely to contract hay fever than their country cousins.

In her studies, von Mutius identified two features of a rural childhood that help to build a kind of immunity to allergies and asthma. One is exposure to the air in cowsheds and barns from a very early age. The other is regular consumption of fresh, untreated milk. Both together reduce the risk that the immune system will overreact to innocuous stimuli: “So children who grow up on small dairy farms are least prone to allergic diseases.”

The positive impact of hay and straw is probably due to the plethora of plant-derived and microbial immunogens that is dispersed into the air when the dairy farmer lays out new straw or milks his herd. The airborne particulates settle on
skin, hair and clothing and contribute to the household dust in the family home. “In particular,” von Mutius notes, “the mattress the child sleeps on acts as his or her personal ‘reservoir’.”

In the context of the GABRIEL study, von Mutius and her team, together with colleagues in Austria and Switzerland, examined nearly 80,000 children living in rural upland regions, and collected dust samples from their bedding. The subjects included both healthy children and youngsters with allergies. The bacteria and fungi present in the dust were analyzed for cell-wall components that are known to modulate allergic reactions. Some of these, such as certain endotoxins, protect against allergies, while bacterial muraminic acids and fungal polysaccharides inhibit the emergence of asthma.

Indeed the researchers also identified those species that exert the greatest protective effect. They inoculated Petri dishes containing various growth media with samples taken on the farms. The microbial colonies that grew on the plates were then tested in a so-called “Western blot” experiment to detect ones that reacted with antibodies present in blood samples taken from farm children. The bacteria that showed the strongest response with antibodies of types IgG and IgA were Acinetobacter lwofii and Lactococcus lactis. The presence of specific IgG and IgA, rather than IgE, antibodies indicates that the immune system is reacting normally to microbial antigens.

When these “probiotic” bacteria were introduced into mice by nasal inoculation, to mimic the conditions encountered by farm children in barn or byre, the animals were found to be less susceptible to asthma than untreated controls. Indeed, inoculation of pregnant mice was sometimes sufficient to protect their offspring. Thus, the progeny of mice that had been exposed to Acinetobacter were less prone to develop asthma than mice born to non-treated mothers. Five years ago, colleagues of von Mutius based at Bochum University founded a company called ProtectImmun, and this start-up firm has begun to use her findings to develop designer microorganisms that confer a degree of protection against autoimmune diseases. Obviously, cells used for therapeutic purposes should not themselves be pathogenic. Fortunately, this is true of Lactococcus lactis, which is a natural constituent of many dairy products.

The second thing that helps protect farm children against allergies is fresh milk. Several epidemiological studies by von Mutius and others have now confirmed this finding. Milk intended for general consumption is routinely pasteurized by heating. This kills pathogens such as EHEC bacteria, which are a particular threat to young children and pregnant women. However, farmers, particularly dairy farmers, view such risks as minimal, and their families and neighbors routinely drink warm milk fresh from the udder. The whole household consumes untreated milk, including the farmer’s pregnant wife and his young children. “The farmers simply argue that it tastes better,” von Mutius explains.

Children brought up on farms are less likely to display symptoms of allergy than their playmates in the same village or children who live in towns.

Source: Jan Greune
Some time ago, her group discovered that children born to mothers who regularly consume fresh milk are able to mount specific immune responses immediately after birth, and soon begin to produce signal molecules that have anti-allergenic effects. To follow this up, the LMU researchers tallied the amounts of fresh milk consumed by farmers’ wives during pregnancy and also analyzed cord blood after birth. “Earlier studies had relied on retrospective surveys of eating habits,” says von Mutius, a method that is less accurate because mothers cannot be expected to remember exactly what and how much they consumed during pregnancy. At all events, it is clear that, for best protection against allergies, children should be exposed as soon as practicable, if possible in the womb, to raw milk or microbes found in farmyard settings.

The question of why raw cow’s milk has such a health-promoting effect is the focus of ongoing research in von Mutius’ laboratory. Clearly, pasteurization eliminates harmless probiotic bacteria, such as lactobacilli or pseudomonads, which colonize the human gastrointestinal tract. The process also alters the protein and lipid composition of the milk, and work carried out during the GABRIEL study has suggested that heat-sensitive proteins present in the skim milk fraction have a markedly positive impact on allergy risk. So here is an effect that is not mediated by the microflora present in cow’s milk. Among the proteins that are thought to be involved are alpha-lactalbumin, beta-lactoglobulin and bovine serum albumin. Whether these proteins or other factors in skim milk dampen the reactivity of the immune system is not yet settled. “Homogenization of the milk may also be problematic, as it strongly alters fats,” says von Mutius, “but the data do not yet permit a firm conclusion.”

Erika von Mutius is collaborating with a commercial partner to develop treatment procedures that preserve potentially health-promoting substances present in raw milk. Alternatively, specific protective factors, such as skim-milk proteins, could be added back after conventional processing. It should be noted here, however, that von Mutius explicitly advises against letting city children drink raw milk.

The GABRIEL study, which lasted from 2006 until 2010, also looked into many other factors that might be correlated with allergy or asthma risk. Researchers ascertained, for example, whether homes were heated with coal or wood, and whether farms were run as a full-time concern or on a part-time basis. They documented the children’s quality of life and determined what sorts of animals they came into contact with. Notably neither tillage nor the presence of horses protects against allergies, von Mutius points out. Farm children were found to have a slightly higher quality of life overall, but this cannot explain the differences in the incidence of allergic disorders. The researchers assume that it is the whole package, the traditional “peasant” lifestyle, which accounts for the farm effect – although incontrovertible proof of this thesis is not yet to hand.

Here, one must remember that neurodermatitis, hay fever or asthma does not result from environmental influences alone. Genetics also has a say in the matter. Thus, farm children who are fully protected from asthma and allergies all carry particular variants of a gene for one of the so-called “Toll-like” receptors. These proteins function as the primary sensors of exogenous substances in the body. They essentially decide whether a given compound is native or foreign, self or non-self.

During the GABRIEL study, von Mutius and her colleagues also identified an
important gene complex, called ORM-DL3, which is functionally associated with asthma risk. “Certain variant forms of this locus correlate with quantitative changes in the level of risk for asthma,” she explains. What the genes in this complex actually do is not yet clear. Early indications suggest that their products are involved in protein folding and may play a role in the metabolism of fats. It is also known that particular versions of ORM-DL3, in combination with regular exposure to cigarette smoke or to certain pathogens, make children more susceptible to asthma. Indeed, predisposing variants at this locus play a major role in one-third of cases of childhood-onset asthma, especially in particularly serious ones, says von Mutius.

She herself is content to leave the task of solving the genetic riddle to basic researchers, and has turned her attention to the question of whether factors other than the composition of the aerial “microbiome” in barns and byres, have a protective effect. She is now investigating nasal swabs taken from subjects who participated in the GABRIEL study to determine the make-up of the bacteria present. “It is possible,” she says, “that some environmental bacteria that colonize the airways displace species that facilitate the development of asthma.” This would mean that particular bacterial cells that occur in hay and straw, not just their surface components, contribute to protection. Alternatively, metabolic products synthesized by bacteria, such as short-chain fatty acids, may modulate how the immune system responds to typical allergens, von Mutius explains. “Of course, all three mechanisms could work together,” she adds.

Nowadays, von Mutius devotes herself mainly to research, although she continues to see patients regularly and spends one week per month on the hospital wards. “That is very important for me; it brings me down to earth,” she remarks. “The parents are the ones who ask the right questions. Epidemiological studies can reveal statistical correlations, but I only believe the ones that make clinical sense,” she says.

Prof. Dr. med. Erika von Mutius is Professor for Pediatric Allergology and Senior Consultant in the Dr. von Hauner Children’s Hospital at the Medical Center of Munich University, and heads the Outpatient Department for Asthma and Allergies. Born in 1957, von Mutius studied Medicine at LMU Munich, qualifying as a consultant pediatrician in 1992. She then moved to the University of Arizona in Tucson (USA) to take up a research position. In 1996, she obtained board certification as an allergologist, and completed her Habilitation in 1996. In 2013, von Mutius received a Leibniz Prize from the German Research Foundation (DFG), the most important accolade awarded for research achievement in Germany.