

Dirt and infections don't just make you less allergy-prone, they can fight off some cancers too. Jessica Marshall reports

Filthy healthy



IT WOULD be wrong to call dairy farming a shit job. But workers on dairy farms do have to deal with vast quantities of manure. In fact, they inevitably end up breathing in a lot of dust consisting largely of dried manure, along with all the bacteria that grew in it. That sounds unhealthy, and in some ways it is, but it does have one benefit: dairy farmers are as much as five times less likely to develop lung cancer.

As strange as it sounds, epidemiologists are starting to uncover some unexpected links between our exposure to dirt and germs, and our risk of cancer later in life. Children who attend daycare in their first few months are much less likely to develop leukaemia than those who stay at home, for instance, while some tuberculosis vaccines reduce the risk of skin cancer. Such findings point towards a curious possibility: one way to avoid dying of cancer may be a hefty dose of germs.

The notion that living dirty has benefits may ring a bell. Researchers have been debating the "hygiene hypothesis" for years, but it is typically discussed as an explanation for the rising incidence of allergies and asthma in developed countries, not cancer.

The idea is that our immune systems evolved to conduct a ceaseless war on pathogens, parasites and other microbes, but modern lifestyles mean we face fewer threats. This throws our immune systems out of kilter, making them prone to overreact to certain stimuli like pollen or peanuts.

Now some researchers are starting to wonder whether the higher incidence of certain cancers in affluent populations – including breast cancer, lymphoma and melanoma – might also have something to do with sanitised, infection-free living. If they're right, the implications are huge. If we can understand exactly what it is about some germs that has a protective effect, we should be able to reduce people's risk of developing certain tumours later in life by exposing them to harmless microbes.

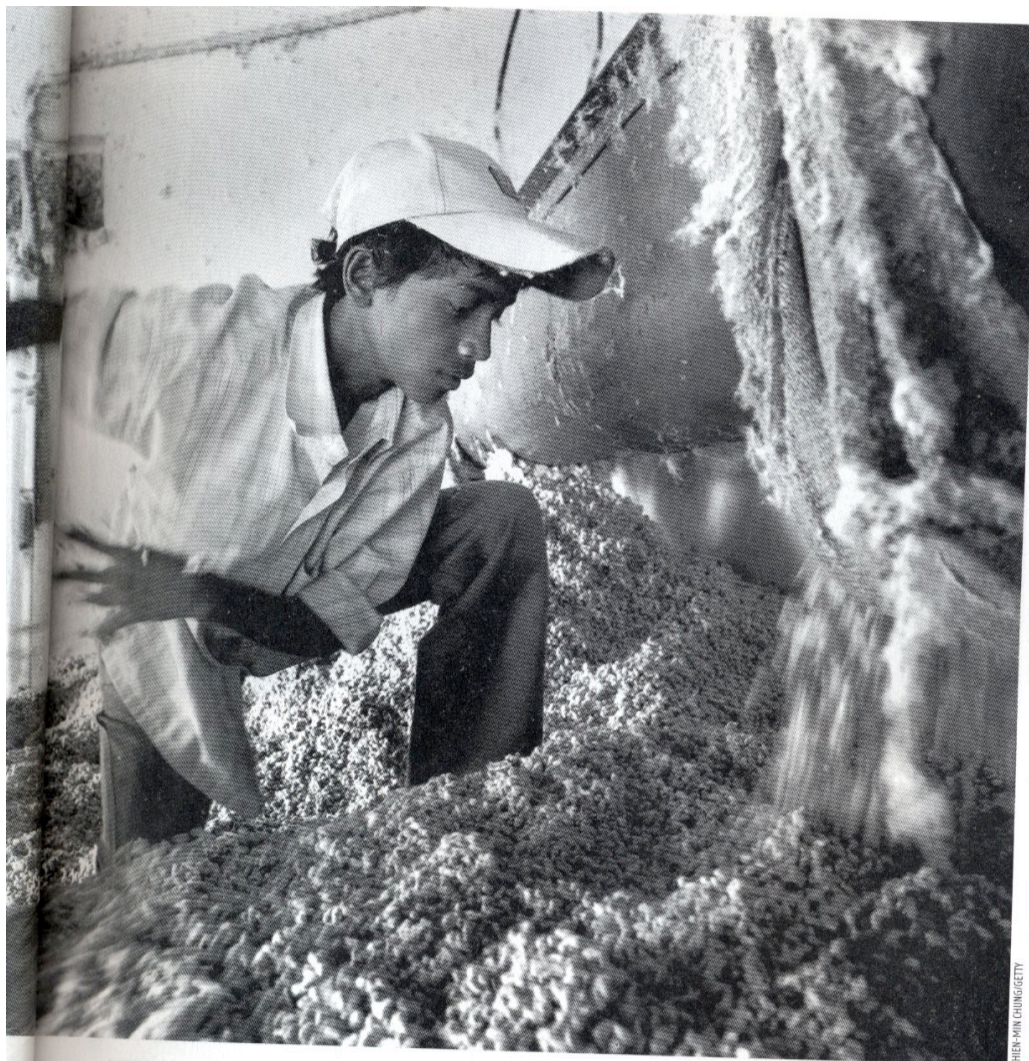
This might seem surprising, given that some viruses can undoubtedly cause cancers. Yet with a few childhood cancers it has long been suspected that the risk of developing them is reduced by exposure to infections early in life. Recent studies have confirmed that children who have social contact outside the home early on, such as attending daycare,

have a reduced risk of both childhood leukaemia and Hodgkin's lymphoma as young adults. Others have found that kids with more older siblings have less chance of developing Hodgkin's lymphoma, says Ellen Chang of the Northern California Cancer Center in Fremont, who carried out some of the studies.

It is not just childhood exposure that matters, though. As long ago as the 1970s it was noticed that workers in cotton factories have surprisingly low rates of lung and some other cancers. One explanation is that they owe the favour to cotton dust. This contains lots of endotoxin, a lipopolysaccharide found in the cell walls of many bacteria, which might keep the immune system on high alert.

A series of recent studies by Harvey Checkoway at the University of Washington, Seattle, supports this idea. His team looked at cancer rates among female cotton textile workers in Shanghai, China, where detailed records reveal past exposures to endotoxin. Those with higher and longer endotoxin exposure on the job had a lower incidence of many cancer types, including lung, breast, liver, stomach and pancreatic cancer.

Endotoxin could also explain the



Working in a cotton factory protects you against lung, breast, liver and other tumours

Tackling cancer

Immune stimulation by bacteria and viruses may do more than just prevent some cancers. It might even be able to cure some tumours. Some of the first attempts at this were carried out in the 1890s by American doctor William Coley, who treated cancer patients with heat-killed bacterial preparations. Several groups are now trying to revive his methods.

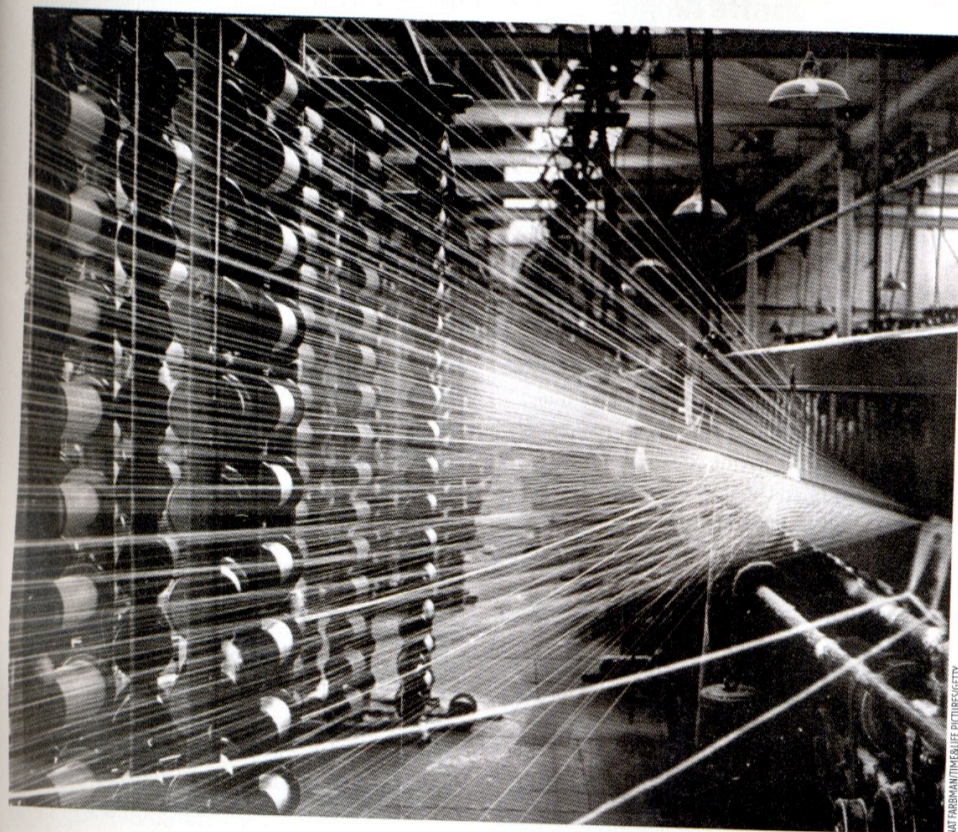
MBVax Bioscience in Ancaster, Ontario, Canada, is reintroducing Coley's preparation. It plans to conduct clinical trials, and claims that in initial studies 24 out of 38 patients with advanced cancer have shown signs of regression. Meanwhile, Coley Pharmaceuticals of Wellesley, Massachusetts, is trying to develop drugs that trigger the same immune response as some bacteria. It hopes to use these drugs to treat cancer, allergy and asthma.

John and Cynthia Stanford at University College London have been treating cancer patients with injections of heat-killed *Mycobacterium vaccae*, a relative of the tuberculosis-causing bacterium. "If you don't understand the immunity, it sounds a bit like magic herbs, but it's straight immunology," John Stanford says.

While a clinical trial by another group failed to find any survival benefit for patients with non-small-cell lung cancer, Stanford claims there were serious problems with that trial's execution. A reanalysis by Stanford and others, grouping the subjects by lung cancer type, found that for those with adenocarcinomas, survival times increased by four-and-a-half months. The results will appear in the *European Journal of Cancer*.

One major problem for all such studies is that ethical guidelines require new treatments to be given alongside the best available treatments, namely chemotherapy and radiation. Since these conventional therapies suppress the immune system, they might keep the immune approach from working.

Perhaps the most surprising finding of the initial trial, though, was that the quality of life of the people receiving *M. vaccae* improved in nearly all measures – including cognitive functioning, vitality and pain. Christopher Lowry of the University of Colorado, Boulder, has found that injecting rats with *M. vaccae* activated serotonin-producing neurons in part of the brain (*Neuroscience*, vol 146, p 756). This raises the intriguing possibility that *M. vaccae* could work as an antidepressant.



If you breathe in lots of aerosolised manure, you are far less likely to develop lung cancer

reduced risk of lung cancer among dairy farmers found by several studies in various countries. For instance, Giuseppe Mastrangelo of the University of Padua in Italy and colleagues found that dairy workers in the province were far less likely to get lung cancer compared with their peers who worked in fields or orchards (*Indoor and Built Environment*, vol 13, p 35). The greater the number of cows, the greater the protection. Even smokers gained some protection: smoking dairy farmers were less likely to get lung cancer than smoking non-dairy farmers.

Thankfully, though, breathing in aerosolised manure is not the only way to pump up one's cancer-fighting immune patrol. Certain childhood vaccines also seem to do the trick, at least for the deadly skin cancer melanoma.

There have been various attempts over the past century to treat cancers such as melanoma with live viruses or bacteria, with



saved many people from developing melanoma in the past and, on this basis, their reintroduction might even be justifiable," the team concluded (*European Journal of Cancer*, vol 39, p 2372).

Further analysis showed the risk falls even more among immunised people who have also had a serious infection with a fever. What's more, among people who did develop melanoma, these vaccinations also reduced the risk of dying of it.

to viruses and bacteria – through infections, vaccinations or proteins such as endotoxin – stimulates the immune system and boosts its anticancer activity. This makes sense, since we now know the immune system plays a bigger role in battling cancer than previously thought, destroying many tumours at an early stage or keeping them in check.

Transplant patients taking immunosuppressing drugs are 3 to 4 times as likely to develop melanoma, for instance, while genetically engineered mice missing key immune genes rapidly become riddled with tumours. More evidence comes from studies like that of Lin Zhang of the University of Pennsylvania in Philadelphia, who reported in 2003 that patients whose ovarian tumours contained immune cells had a 38 per cent chance of surviving at least five years, compared with just 5 per cent for those whose tumours contained none.

"Turned around, it means that the normal, healthy immune system is capable of suppressing the development of spontaneous tumours, at least to a certain degree, for quite a while," says Uwe Hobohm of the University of Applied Sciences in Giessen, Germany.

A related possibility is that substances such as endotoxin can act as an adjuvant, which is a substance added to vaccines to boost the strength of the immune response. The most important part of any vaccine, of course, is a protein specific to the disease you are trying to protect against – called the antigen – so the immune system can learn to target that protein. But vaccine makers learned long ago that generating a strong enough response to an antigen often requires an adjuvant too.

"The focus is always on the antigen, but

"Thankfully, inhaling dried manure is not the only way to boost cancer-fighting activity"

mixed results. Klaus Kölmel of the University of Göttingen in Germany knew of these, and it made him wonder whether vaccinia, the virus used to vaccinate against smallpox until the 1970s, or the BCG vaccine against tuberculosis, might have a protective effect.

His team compared the past vaccinations of 603 people who had melanoma with those of 627 controls. Overall, people who had received either the TB vaccine as a baby, or the smallpox vaccine, or both, were up to 2.5 times less likely to develop melanoma. In those under 50 years old, the risk dropped fourfold, which suggests that the protective effect of the vaccines weakens with age. "Vaccinia and neonatal BCG vaccinations seem to have

The timing of vaccination seems to matter, as only people given the BCG as babies had a lower risk. The strain of the vaccine seems to be important, too. In one centre used in Kölmel's study, in Dijon, France, BCG did not confer melanoma protection. This centre was the only one to use the Pasteur Institute strain of the vaccine.

Given that few studies of this kind have been done, it is possible that other vaccinations or diseases also reduce the risk of cancer. The key question, of course, is why. Despite growing evidence of the effect of exposure to infection on cancer risk, researchers are divided on the mechanism.

The simplest explanation is that exposure



Attending daycare early in life or having older siblings protects kids against leukaemia

you need both," Hobohm says. "In cancer, usually you don't have both. You only have the antigens." When the adjuvants come along, they might trigger T-cells, which may already have detected cancer antigens, to start attacking cancer cells.

Others believe that exposure to infections rebalances the immune system, which gets out of whack in their absence. "When you get cancer, it means that your immune system is not recognising that cancer as danger. When you expose patients to bacteria you're reprogramming the immune system by altering the immune regulatory network," says John Grange of University College London, who has worked with both Kölmel and Mastrangelo. Imbalances in this network can lead to abnormal immune responses like allergies and asthma, he says.

Hobohm points to yet another possible mechanism: fever. "The effects of bacteria on the immune system are enhanced by the fever," he says. The idea goes back over a century. In the 1890s, American doctor William Coley attempted to treat cancer – sometimes successfully – with heat-killed bacterial preparations, inducing a reaction that often included high fevers.

Kölmel's study also found that fevers are associated with a lower melanoma risk. The idea makes sense because cancer cells are more vulnerable to heat than normal cells, Hobohm says, and dying cancer cells produce extra antigen that can be recognised by the immune system, sounding the alarm louder.

In melanoma, there may be a rather more specific mechanism, dependent on an ancient viral gene lurking in our genome. In the distant past, some retroviruses managed to

insert their genetic material into human germline cells, and their genes have been part of our genome ever since. Many studies have suggested there is a link between these human endogenous retroviruses (HERVs) and some cancers. "There are a few cancers which are associated with HERVs," says Bernd Krone of the University of Göttingen in Germany, who worked with Kölmel on the melanoma study.

Triggering an attack

While the role of HERVs in cancer is still being debated, it is clear that HERV genes get turned on in certain cancers. In particular, melanoma cells produce lots of a protein called HERV-K-MEL, and the TB bacterium, the vaccinia virus and other pathogens all produce proteins containing very similar sequences to HERV-K-MEL. The immune response to these pathogens would thus also trigger an attack on any cells producing HERV-K-MEL, stopping melanomas before they start, Krone believes (*European Journal of Cancer*, vol 41, p 104).

Whichever of these mechanisms proves to be correct, it is clear that exposure to viruses or bacteria does not prevent all kinds of cancer. Although the incidence of many cancers was reduced in Checkoway's studies of Shanghai cotton textile workers, other types of cancer were unaffected. Even with the affected cancers – lung cancer for instance – the improved immune response may only beat back certain subtypes. And some studies suggest infections might increase the risk of a few cancers such as non-Hodgkin's lymphoma, though the results are mixed.

Nevertheless, the natural question that arises from these findings is whether

exposure to viruses and bacteria, or their proteins, could be used systematically to prevent certain cancers – or even to treat them (see "Tackling cancer", page 35). "My hopes are for prevention," Krone says.

There are of course huge problems. Assessing ways of preventing cancer, rather than treating it, can take decades. And no one is suggesting deliberately exposing people to risky infections, or to cotton dust or manure. When it comes to vaccines with a proven safety record, however, there are far fewer issues. After all, if Kölmel is right about the protective effect of the BCG and smallpox vaccine, we already have the means to reduce the risk of melanoma.

Smallpox vaccination ended in the 1970s – although it resumed for US military personnel in 2002 – while the BCG vaccine was dropped by many countries in the 1990s. (Others, such as the US, have never used it due to its variable efficacy.) The UK and Australia, for instance, now give the BCG vaccine only to babies in high-risk areas.

The ending of vaccination doesn't explain the steady rise of melanoma in western countries in recent decades. Rather, Kölmel calculates that the protective effect of the TB and smallpox vaccines will begin to "wear off" around 2010 as those who were born after these vaccinations were stopped get old enough to develop melanoma.

Kölmel, Grange, Krone and colleagues have just completed a trial using the widely available yellow fever vaccine – another live vaccine – to see if it offers the same cancer protection as smallpox and TB vaccines. They also expanded their analysis in this trial to include several other types of cancer.

It is too early to know whether it was successful, but it will be good news for all of us if it is. In the meantime, when you find yourself suffering from flu, or yet another cold, console yourself with the thought that it might just be reducing your chances of getting some cancers. And maybe a trip to a dairy farm wouldn't hurt, either. ●

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