Mystery cancer: Inside the villages of the damned

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What can explain the mysterious "houses of death" in Turkey? The answer may raise concerns across the world

WHEN Michele Carbone first visited the Cappadocia region of Turkey, he was struck by the beauty of the volcanic landscape, sculpted by wind and rain into picturesque caverns and rock towers. But the mountains hid a dark secret: some of the villages appeared to be cursed.

The inhabitants are plagued by a particularly nasty form of cancer, called mesothelioma. "When we wake up, we see if we've got a cough, because whoever coughs is considered ready to die," one of the villagers told Carbone. "If we see somebody cough when they're walking in the street, everybody looks at them and thinks they will be next."

People in neighbouring settlements shun those from the "cancer villages" in case their condition is contagious. Some villagers emigrate but not everyone wants to or can afford to – and anyway, some suspect that leaving will not save them from their "fate".

Carbone, a pathologist at the University of Hawaii Cancer Center, was in Cappadocia to understand the origin of the villagers' illness. Mesothelioma usually occurs in people who have been exposed to asbestos, yet that is not the case here. For four decades scientists and doctors have been trying to solve this puzzle, and in the past few years the answers have started to emerge.

It's not just Cappadocia that will benefit. Asbestos products are now banned in most developed countries, but since this form of cancer takes decades to develop, the number of cases in these nations is still climbing. A similar fate awaits those still using the mineral. Finding out what's behind the cancer villages may reveal the way that this disease develops and perhaps even point to effective treatments.

What's more, the work has revealed a new source of cancer risk that could affect people around the globe. "It doesn't take a genius to figure out that in 30 or 40 years we're going to have a problem," Carbone warns.

A better understanding of mesothelioma is certainly needed. It is one of the deadliest cancers; people tend to live for about 12 months after diagnosis. The tumours form within the lining of the lungs, leading to an "absolutely horrendous" death, says Julian Peto, an epidemiologist who helped to demonstrate the need for restrictions on asbestos use in the 1970s.

It is the very quality that makes asbestos so useful – its extreme durability – that makes it so deadly. Once inhaled, its microscopic dust settles deep within the lungs and cannot be broken down by the body's normal clean-up mechanisms. Over time this leads to inflammation and eventually cancer.

Doom cohort

Asbestos was once a common building material, and so it is people who were in the construction industry between the 1950s and 80s who are most at risk in the West. As these people age, the prevalence of mesothelioma climbs. It is expected to peak in 2016 in the UK, for instance, at nearly 2500 deaths a year. "There's a doom cohort falling off the graph," says Peto, now at the London School of Hygiene and Tropical Medicine.

While asbestos is still mined in some countries, such as Russia and India, those that had banned the stuff could rest easy knowing that they had uprooted the cause of the cancer. At least, that was how it seemed before the recent discoveries in Cappadocia.

It was in the 1970s that a doctor from Ankara was called in to investigate the strange deaths in Cappadocia. The cancer villages are remote; a 5-hour bus journey from Turkey's capital. The soil is poor and the climate harsh, and most people work on the land or make ceramic pottery to sell to tourists. There was a saying about one of the villages: "The peasant of Karain falls ill with pain in the chest and belly, the shoulder drops, and he dies."

As well as helping those villagers with cancer as best they could, the doctor's team questioned the village leaders about the pattern of deaths. They established that in the three worst-affected villages, mesothelioma caused between a third and a half of all deaths. "That's mind-boggling," says Aubrey Miller at the US Environmental Protection Agency, who was later called in to help. "There's nothing else I can think of that has that level of disease associated with it."

Naturally the first thought was that people were somehow being exposed to asbestos. There was no asbestos mine nearby, but a small amount of the mineral was found in the whitewash on people's homes. A more detailed investigation showed, however, that there was no more asbestos in the cancer villages than in neighbouring hamlets.

Instead, the answer lay in the surreal volcanic landscape that is such an attraction to tourists. It hinges on a little-known fact: there are many more kinds of asbestos-like compounds than those that, strictly speaking, qualify for the name. The term asbestos was the commercial name given to six similar compounds that are all silicates: they can be sodium, magnesium, calcium or iron silicate. In nature, there are another 390 silicate minerals that also form the fine, durable dust that is so dangerous when inhaled. It is one of these compounds that is killing the people of Cappadocia.

The substance in question is called erionite and parts of Cappadocia are riddled with it. The erosion of this soft, white rock produces the picturesque chimneys and caverns so characteristic of the region. The three cancer villages happen to be near erionite outcrops, and since the rock is easy to quarry and carve up into blocks, the villagers have used it to build their houses.

That is where the story had got to by the time Carbone came along, but there was still a question: why did the disease seem to affect the inhabitants of some houses more than others? These houses appear cursed, with nearly all the inhabitants succumbing, one by one.

The working theory was that these so-called "houses of death" had been made from stone with more dangerous forms of erionite. Yet after the buildings were pulled down, the rubble was left where it fell, crumbling into white dust that blew around the streets. That should have exposed everyone in the village to the danger, but people in these families were still much more likely to

develop cancer.

So Carbone set up a table in the village square and began interviewing residents about every aspect of their lives: what they ate and drank, where they worked, their medical background and family histories. His first hypothesis was that people needed two risk factors to get sick: as well as being exposed to erionite they also had to be infected with a virus called SV40, which may be a contributor to asbestos-caused cancer. But biopsies came back with no trace of the virus.

The villagers' family trees proved more fruitful, suggesting that there could be a genetic basis for the disease. This was a difficult inquiry to pursue, though, as there was no official register of births and deaths and the limited family histories only recorded people's fathers, ignoring the maternal line.

As the evidence accumulated, Carbone and his team published a paper in 2001 using data from six generations of families (*The Lancet*, vol 357, p 444). The pattern of disease suggested that a single gene raises vulnerability to mesothelioma in these people. The tendency for several generations to live in the same house could be what made it seem like certain homes were blighted.

The villagers weren't happy, though: they felt stigmatised. And other scientists accused the team of publishing their results too soon, as they had not yet identified the gene. In addition, the inheritance pattern didn't look quite right; a few people who were born elsewhere and had married in still got cancer.

Further detective work has eliminated some of the inconsistencies in the inheritance pattern. Some of those who had married in turned out to come from families with their own history of mesothelioma. The gene may be common in the area because isolation has led to high rates of intermarriage. "A lot of those folks are greatly related," says geneticist Joseph Testa at Fox Chase Cancer Center in Philadelphia, Pennsylvania, who worked with Carbone. And even people without the gene may eventually get the cancer simply because there is so much erionite floating around.

While the study attracted criticism, it nevertheless helped the team secure funding to continue studying the Cappadocians. It also allowed them to investigate two families in the US with high rates of mesothelioma, as well as certain other cancers, who didn't have an obvious source of asbestos exposure.

That work came to fruition in 2011, with the discovery that members of both American families have a mutation in a gene called *BAP1*. This gene normally acts as a brake on cell division, and so it makes sense that the mutated form leads to the excess cell growth that causes tumours.

This mutation seems to be a rare one, though, and it is not to blame in most people who get mesothelioma – including those in Cappadocia. Although the particular gene or genes implicated in the "houses of death" remains unknown, the US finding does suggest that the hunt will eventually pay off. "This is the first concrete evidence that a person's genetic make-up can affect susceptibility to this cancer," says Testa.

Indeed, he thinks there are probably many genes that affect our vulnerability to mesothelioma. That would explain why some people get the cancer after very little contact with asbestos, while others stay healthy after alarmingly high exposure. "I know asbestos workers that told me they

threw asbestos snowballs at each other – and they never had mesothelioma," says Testa.

As well as helping to shed light on the genetics of cancer, the Cappadocians' plight also raised the red flag about the danger of erionite. Animal research suggests that, if anything, erionite is more likely to cause cancer than asbestos.

The mineral, which is formed by the action of water on volcanic ash, has been found in mountainous or rocky areas all over the world. In the US, concerns were first raised in North Dakota, where erionite is present in the western Killdeer mountains.

Over the past few decades gravel from these mountains has been used to surface roads, car parks and playgrounds in the sparsely populated Dunn County. "I don't think they know where all that gravel's gone," says Aubrey Miller, who helped run an Environmental Protection Agency investigation into the issue.

Since the EPA stepped in, the state has paved over most of the problem playgrounds and car parks, but some of the roads remain contaminated. As the road gravel gets worn away, it is being topped up with safe gravel, but some erionite must still be there, lurking underneath, and there are no current plans for a clean-up operation.

Many of these highways have seen a sharp increase in traffic thanks to the state's recent oil boom. Some roads that were barely used now have thousands of trucks a day churning up the dust. "If it was asbestos, there would be more public alarm," says Miller.

As yet, Dunn County doesn't seem to have a higher rate of mesothelioma than anywhere else in the US, but Miller points out that it is still early days for a cancer that takes decades to develop. Ominously, in 2010 the EPA found that two of the region's road workers had the beginnings of scars in their lungs similar to those caused by asbestos.

Outside of Dunn County, erionite deposits have so far been found in two other counties of North Dakota, as well as 12 other states. It has also been discovered in parts of Europe, Australia and New Zealand (see "A global concern"). As erionite has only recently come to our attention as a hazard, there is little information on which communities are at risk.

And what about the other 400 or so fibrous silicate minerals that exist in nature? "This whole group of minerals is a potential cause of concern but we just do not know enough about them yet to judge the risk," says Miller.

One thing we do know is that the problem of "traditional" mesothelioma, caused by asbestos, is going to be around for many more years to come. The Cappadocians and the US mesothelioma families may help point the way to better treatments, as clinical trials are quicker and easier when the volunteers have a high rate of the disease in question.

The main reason mesothelioma is so deadly is that it is usually only diagnosed at an advanced stage, when it is too late to cut it out of the chest without damaging vital organs. A blood test for compounds released by the cancer when it is still small might allow it to be detected early enough to be removed; one such compound was discovered a few months ago.

There may even be a way of spotting people with the *BAP1* mutation with the naked eye. It was reported last year that two-thirds of people with the faulty gene have multiple benign skin growths that look like small fleshy warts, which are otherwise rare. "Clinicians need to be more

aware of this symptom," says Testa.

As this work continues, it is already helping the residents of Cappadocia in a more direct way. They are gradually being moved away from the danger, so at least future generations will be spared. Of the three worst-affected villages, the biggest has been rebuilt in a new location, and a second village is in progress.

Carbone still visits the villages; he has friends there now and likes to go walking through that amazing landscape. But he can never completely relax. Writing of his experiences, he has said that "it is impossible to hold a baby without wondering if she or he will experience the same fate as the man you heard screaming a minute ago. It is impossible to forget any one of the patients."

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