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SCIENCE AND SOCIETY

A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes

Michele Carbone, Salih Emri, A. Umran Dogan, Ian Steele, Murat Tuncer, Harvey I. Pass and Y. Izzettin Baris

Abstract | In Cappadocia, Turkey, an unprecedented mesothelioma epidemic causes 50% of all deaths in three small villages. Initially linked solely to the exposure to a fibrous mineral, erionite, recent studies by scientists from Turkey and the United States have shown that erionite causes mesothelioma mostly in families that are genetically predisposed to mineral fibre carcinogenesis. This manuscript reports, through the eyes of one of the researchers, the resulting scientific advances that have come from these studies and the social improvements that were brought about by both the scientists and members of the Turkish Government.

Mesothelioma is a cancer arising from the mesothelial cells that line the pleural, pericardial and peritoneal surfaces[1,2]. Although there are rare benign variants of mesothelioma, such as multicystic mesothelioma or mesothelioma of the atrioventricular node, which are not related to asbestos exposure[1,2], this article focuses on the relatively more common malignant mesothelioma. In the United States there are approximately 2,500 cases and deaths per year of malignant mesothelioma, which is often related to asbestos exposure (BOX 1). Median survival is approximately 1 year from diagnosis because current therapies have only marginal effects in altering the natural course of the disease[1]. Although the link between asbestos exposure and mesothelioma was established in 1960, it is still unclear whether all types of asbestos cause mesothelioma[3–6] (BOX 2).

Mechanisms of mineral fibre carcinogenesis

The mechanisms of mineral fibre carcinogenesis have been studied prevalently using crocidolite asbestos, and are summarized below. Carcinogenesis as a result of exposure to crocidolite has been linked to its ability to induce the expression of both tumour-necrosis factor-α (TNFα) and its receptor (TNFR1) in mesothelial cells and in macrophages that phagocytose asbestos[7]. Indeed, *Tnfr1* knockout mice do not develop fibroproliferative lesions after asbestos

Box 1 | **Asbestos and mesothelioma**

Mesothelioma was rare until the second half of the twentieth century[47]. In 1960, C. Wagner reported a mesothelioma epidemic among crocidolite asbestos miners in South Africa[48]. After the report from Wagner, the link between asbestos exposure and mesothelioma remained controversial over the following decade. Epidemiological data (reviewed in REF. 34) and experiments in animals supported this association (reviewed in REF. 49). Eventually, the argument was settled in the scientific community, and the idea that people exposed to asbestos had an unusually high incidence of mesothelioma was accepted[50–52]. However, the debate still persists on whether all types of asbestos cause mesothelioma. There are, in fact, two main types of asbestos. The first type, amphibole asbestos, includes the minerals crocidolite, amosite, tremolite, anthophyllite and actinolite. The second type, serpentine asbestos, is also called chrysotile. According to some experts, only amphibole asbestos, particularly crocidolite and amosite (which were mostly mined in South Africa), causes mesothelioma. Chrysotile (which is still mined in some countries) does not cause the disease, and mesotheliomas associated with chrysotile exposure are probably caused by the frequent contamination with tremolite[3]. Other experts, however, argue that chrysotile is as dangerous as amphibole asbestos and consider chrysotile the main cause of mesothelioma in the developed world, because it accounts for about 90% of all exposures[4] (BOX2). A review of the literature on this topic revealed that the data were so diametrically different that it was not possible to reconcile these contradictory findings[5].

The median latency from time of asbestos exposure to disease development is about 32 years and ranges from 20 to about 50 years[1,2,34]. Early diagnosis (stage 1A) and surgical treatment are often associated with prolonged survival of ≥5 years, but less than 5% of mesotheliomas are diagnosed at this early stage[1]. By the time patients develop clinical symptoms, usually dyspnoea (difficulty in breathing) and pain, and seek medical attention, the disease is well advanced and incurable[1,53].

exposure[8]. Crocidolite induces cell lysis and apoptosis[9], however, asbestos-induced TNFα secretion activates nuclear factor-κB (NF-κB) that protects mesothelial and other cells from crocidolite-induced cell lysis[7]. Therefore, asbestos-damaged mesothelial cells divide rather than die and can propagate the genetic damage[7] that is induced by mutagenic oxygen radicals released by mononuclear phagocytes that have ingested asbestos[10–13]. Moreover, asbestos induces the phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2), which leads to the activation of the transcription factor AP1 and stimulates cell division[10]. Activation of this pathway can also promote cell invasion by causing the induction and release of cellular metalloproteinases[14]. Whether other types of asbestos and mineral fibres are carcinogenic owing to the same mechanisms is under investigation.

Mesothelioma is rare between cohorts that are not exposed to asbestos, but it is frequent in workers who are exposed to it. For example, 4.6% of South African crocidolite asbestos miners who had been exposed to asbestos for more than 10 years developed and died of mesothelioma[15]. This finding highlights the risk of this disease among asbestos workers, and at the same time shows that only a fraction of heavily exposed individuals develop mesothelioma. In contrast to other carcinogens there is no linear dose–response relationship between asbestos exposure and the incidence of mesothelioma[2]. Above a certain threshold additional exposure does not seem to proportionally increase the risk of developing mesothelioma. Instead, some people seem more susceptible than others[2]. Most studies report that about 80% of mesotheliomas develop in asbestos-exposed individuals[5]. However, the association of exposure with the development of mesothelioma varies from about 10% to 100% depending on the article and on the criteria used to establish whether exposure has occurred[5].

The obvious question that arises from these studies is whether there are cofactors that make some individuals more susceptible to asbestos carcinogenesis. We found that genetic predisposition to mineral fibre carcinogenesis has led to an epidemic of this disease in Cappadocia, Turkey, and also in some US families[16,17]. We also found that simian virus 40 (SV40) functions as a co-carcinogen with crocidolite asbestos in causing mesothelial cell transformation[18]. SV40 can also induce the development of mesothelioma in hamsters exposed to crocidolite, and it lowers the amount of crocidolite that is required to cause the disease[14]. Crocidolite–SV40 co-carcinogenesis has been independently verified[19–22]. Experiments are in progress in our laboratory to investigate whether co-carcinogenesis extends to other mineral fibres. So far, our studies indicate that genetics and viral infection influence mineral fibre carcinogenesis and that the risk of mesothelioma in individuals exposed to asbestos and erionite varies depending on their genetic background and possible exposure to other carcinogens.

In this Science and Society article M.C. discusses the sequence of events, obtained with his co-authors, that have linked genetic predisposition to mineral fibre carcinogenesis in some villages in Cappadocia, Turkey. In addition to the scientific results, some social issues concerning this work are also discussed.

Box 2 | **Economic issues related to asbestos and mesothelioma research**

After 40 years of research on whether chrysotile does or does not cause mesothelioma, the issue is still unresolved, and the controversy is stronger than ever[6]. The argument is not purely scientific: the economic implications of linking chrysotile or any other agent to mesothelioma are enormous because of litigation[54], and chrysotile production is a major source of revenue for some countries. The most prominent example of economic versus scientific argument is seen in the United States, where, up until 2002, defendants had paid out US$54 billion in asbestos-related claims and the estimated future liability ranges from $145 to $210 billion[54]. Asbestos victims, however, have received less than half this money, because over 50% of the money is spent in transaction costs, mostly attorney fees[54]. Because most asbestos-containing products were banned from the marketplace in the 1970s, it had been predicted that the incidence of asbestos-related diseases would decrease and the claims would decline. However, the volume of new asbestos cases and the costs of litigation continue to increase[54]. Because of this, any research that seems to link any factor other than asbestos to mesothelioma pathogenesis becomes invariably controversial, like chrysotile, which some experts believe was erroneously included in the asbestos family because it has significant mineralogical and biological differences compared with amphibole asbestos. Recently, the research linking simian virus 40 (SV40) to mesothelioma has also caused problems because SV40 contaminated early polio vaccines; therefore vaccine manufacturers have been dragged into litigation.

The published literature reflects these conflicts of interest and it is difficult to identify articles that might have some bias from those that do not. Our studies on erionite and genetic predisposition to mineral fibre carcinogenesis have not been controversial, probably because the problem seems localized in Cappadocia where litigation is not a factor.

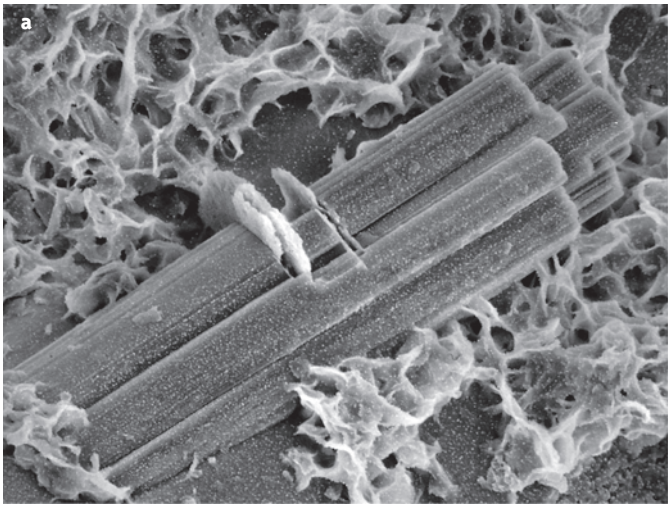

Figure 1 | **Erionite and the village of Karain. a** | A scanning electron microscope image of erionite is shown. Note the individual fibrils (0.5 µm in diameter) forming the erionite bundles (5 µm in diameter). **b** | The village of Karain is shown, where the houses are built with carved blocks of stone quarried from the erionite-containing rock from the nearby mountain and river.

A mesothelioma epidemic in Cappadocia

In 1978, Y.I.B. discovered an unprecedented epidemic of mesothelioma among three villages, Karain, Tuzkoy and Sarihidir, which are located in Cappadocia, Turkey[23,24]. Selikoff and co-workers proposed that the epidemic was caused by exposure to asbestos[25], but subsequent studies by Y.I.B. and colleagues demonstrated that asbestos had little if anything to do with this epidemic[26,27]. Tremolite and chrysotile asbestos are commonly found in Turkey (as components of the white stucco used to cover the walls of many houses, for example), but these minerals are rare in these three villages — they are present at levels that are comparable to the levels detected in other villages nearby in which mesothelioma does not occur[26]. Instead, mineralogical studies and analyses of lung content showed the presence of a fibrous mineral called erionite, a zeolite group mineral that has some physical properties similar to crocidolite[27,28] (FIG. 1a). Erionite is contained in the zeolite stones that are used to build houses in these three villages (FIG. 1b). Traces of erionite have been detected in the air in these villages and it has been proposed that inhalation of even minute amounts of erionite is sufficient to cause mesothelioma[29] (BOX 3). This hypothesis is supported by data showing that inhalation of erionite caused mesothelioma in 27 out of 28 rats, whereas other types of asbestos induced only 11 mesotheliomas in a study of 648 rats[30]. These findings led the International Agency for Research on Cancer to conclude that erionite is the cause of the mesothelioma epidemic in Cappadocia[31]. Only later was it shown that erionite is highly mutagenic in cultured cells[32], and that it induces AP1 activity[33], triggering a pathway that numerous studies have linked to the carcinogenicity of asbestos[10,14]. Therefore, there are at least two minerals that can cause mesothelioma: asbestos and erionite. Curiously, erionite is present in many parts of the world. For example, the largest and purest deposits are found in Nevada, Oregon and California in the USA, and erionite is found also in Japan, New Zealand and in several European countries[31]. However, except for Cappadocia, nowhere else in the world has erionite exposure been linked to the development of mesothelioma. Therefore, the issue of erionite and mesothelioma remained a curiosity that was only discussed in specialized textbooks.

In 1997, I was invited by Y.I.B., who was then chief of the Department of Pulmonary Medicine at the University Hacettepe in Ankara, Turkey, and by his associate, S.E., to present a lecture at the Turkish Lung Society Meeting, which was held in Ankara. I had never met Y.I.B., but I had read about his work in the three villages. I asked Y.I.B. and S.E. whether I could visit these villages and they agreed. Y.I.B. had dedicated the previous 20 years to helping the people of these villages. He had bought them medicines, school supplies and food, never charging a patient, and he had argued with the administrators in various hospitals that they should provide the villagers with mesothelioma with free medical care.

The mesothelioma villages

Cappadocia is located in Central Anatolia in the south-eastern part of Turkey. The geology of Cappadocia is astonishing and surreal (Supplementary information S1 (box)). The volcanic rocks that dominate this area are composed of zeolite-rich layers that contain the fibrous whitish, soft and friable erionite, among other zeolite minerals (FIG. 1a). The fibrous nature of this material sometimes can be seen with the naked eye as white, soft spots in these rocks.

Karain (FIG. 1b), the first 'cancer village' discovered by Y.I.B. in 1974 is a 5-hour drive from Ankara. The houses of this village are built with stones carved out from the nearby mountains and caves or taken from a nearby river, and therefore they contain various amounts of erionite. In Karain, mesothelioma causes >50% of all deaths. When we visited the village in 1997 about 600 people were living there. However, during the past 10 years many people have died of mesothelioma and others have left Karain hoping to escape their fate. For example, 11 people died from mesothelioma between January and August 2006 and a further 6 people who emigrated from Karain to Europe also died. At present, the village has about 150 inhabitants.

Y.I.B. took us around Karain where in some houses almost everybody had died of mesothelioma, whereas in adjacent houses nobody had died of this disease. I noted the same situation in Tuzkoy and in 'old' Sarihidir, where the 'houses of death', as the villagers have named them, were located immediately next to houses where no cases of mesothelioma had occurred. This was thought to be because there was a different

Box 3 | **Erionite-associated mesotheliomas**

Erionite has been associated only with mesothelioma, whereas asbestos has been definitively linked to the development of mesothelioma, lung cancer (asbestos has a synergistic effect with smoke) and possibly laryngeal cancer[2]. Some evidence indicates that asbestos might also have a role in the pathogenesis of lymphoma and multiple myeloma[55]. Y. I.B. and colleagues investigated the possibility that erionite could cause other types of cancer[56], and some of the results are summarized in the table.

The data show that the carcinogenic effect of erionite is specific for mesothelioma, although in these three villages there might be a non-statistically significant increase in the incidence of some types of cancer compared with the general population[56]. We propose that this specificity could be explained by the presence of a unique genetic alteration in the mesothelial cells of some of these villagers, which makes their cells unusually susceptible to erionite carcinogenesis. The mean age of death for mesothelioma was 50 years[56], compared with >70 years in sporadic asbestos-associated mesotheliomas[1]. In these villages, almost all males (M) are heavy smokers, but females (F) do not smoke (although they are exposed to secondary cigarette smoke). In contrast to lung cancer, smoking does not increase the risk of pleural mesothelioma[57]. The fact that lung cancer incidence was not significantly increased indicates that either erionite, in contrast to asbestos, does not synergize with smoking, or that most people die of mesothelioma before they develop lung cancer. There are no pathological differences in mesotheliomas that develop in Cappadocia compared with mesotheliomas in the developed world. MPEM, malignant peritoneal mesothelioma; MPM, malignant pleural mesothelioma.

	Total deaths	Deaths due to malignancies	MPM	MPEM	Lung cancer	Gastro-oesophageal cancer	Leukaemia–lymphoma
Karain (1970–1994)							
No. of cases	305	177	150	7	4	6	3
M/F ratio	160/145	89/88	76/74	3/4	2/2	3/3	2/1
Tuzkoy (1980–1994)							
No. of cases	432	225	105	60	6	4	4
M/F ratio	235/197	118/107	54/51	22/38	4/2	3/1	3/1
Sarihidir (1980–1994)							
No. of cases	87	32	15	4	8	1	1
M/F ratio	46/41	17/15	7/8	1/3	5/3	1/0	0/1

and more oncogenic type of erionite present in the houses in which people had died of mesothelioma. This, I was told, was supported by the observation that mesothelioma did not occur in every house and that there was the possibility that the levels of some elements, such as sodium, potassium, calcium and magnesium, varied slightly among erionite samples from different parts of the world. It was thought that these subtle chemical differences were responsible for the differences in oncogenicity of erionite from nearby houses and villages, and between Turkish and American erionite. The chemical composition and the details of the crystal structure of the erionite from Cappadocia were, at that time, unknown, and the hypothesis was unproven.

However, this hypothesis did not seem to fit with the parallel hypothesis that minute amounts of erionite in the air were sufficient to cause mesothelioma[28]. Many 'houses of death' have been demolished and their ruins have been left on the ground. Apparently, this was done to prevent people from moving into the abandoned houses and running the risk of developing mesothelioma. The wind blows the dust from these ruins throughout the village, covering, with a whitish erionite-containing dust, the clothes of anyone who spends a few hours there (Supplementary information S2 (box)). As the entire village is exposed to this dust, why does mesothelioma occur mostly among people living in specific houses?

There is another village about 3 km from Karain called Karlik. The houses in Karlik are built with similar material, however, in Karlik the incidence of mesothelioma is effectively zero.

In Karlik I learned that the villagers of Karain, Tuzkoy and Sarihidir live in a state of semi-isolation. Residents of the villages nearby are afraid of being 'infected' by those living in the villages with mesothelioma. I was warned by Karlik villagers not to speak to those from the villages with a high incidence of mesothelioma, or share their meals, because I would become 'weak' and develop cancer. Accordingly, it is difficult for people from the 'cancer villages' to find wives or husbands from outside their village. In Karlik, these fears were reinforced when a woman from Karain married a man from Karlik, and then died of mesothelioma (the only reported case of mesothelioma in Karlik). Some Karlik villagers are now afraid that mesothelioma might spread to their village. The villagers of Karain, Tuzkoy and Sarihidir also have difficulties in selling their produce at the local markets — they often take the bus to Ankara (an 11-hour return trip) to sell their produce. Some villagers emigrated to Ankara or to Europe hoping to escape mesothelioma. Other villagers, however, believe that this is their 'fate' and that leaving will make no difference as they observed that some villagers who emigrated still died of mesothelioma, their bodies being returned to be buried in their home village. In this 'reality', any cough or sickness is seen as a possible sign of mesothelioma.

Tuzkoy, which has a population of about 1,300 had from three to six patients with mesothelioma each time I visited (12 times in total). We saw four patients during my first visit (Supplementary information S3 (box)) and there were three during my last visit in September 2006, an extremely high incidence considering that, although the incidence of mesothelioma in the developed world continues to increase[34], it is still on average about 2–20 per 10^6.

I was considered to be an expert on mesothelioma by these villagers, so people were approaching me asking for help. They thought that I should know how to help them, and I had nothing to offer. Science is about facts, not feelings, and it is highly unusual to express feelings in a scientific article, but feelings are what motivate us to discover the facts. I thought that I had to do something to try to help the villagers, so I got involved, and what should have been a tourist excursion became a major research project.

Figure 2 | **Our office in Sarihidir.** This photograph shows where and how a large part of our work was done. When we set up our 'office', many villagers with different medical conditions, ranging from mesothelioma to dermatitis, sought our advice and helped us to prepare the family pedigrees. We never saw patients alone, family members were always present and actively discussed patients, symptoms and our proposed treatments. Clockwise from left, Y. Ozdogan, who is our key worker in Sarihidir, M.C., Y. I.B., a patient, her niece and her son (standing), and S.E.

Is erionite the only cause?

The trip to Cappadocia changed my perspective about this epidemic, I thought that erionite was not the only cause of mesothelioma. I convinced S.E. to work with me, and Y.I.B. gave his approval. We recruited a Ph.D. student to help S.E., and together we accumulated all possible information about the villagers of Karain and Tuzkoy: what they ate and drank, what they did, where they worked, where they lived, their family pedigrees, causes of death, and so on. I also had an alternative hypothesis: that SV40 infection, in combination with erionite exposure, was the cause of this mesothelioma epidemic. We had previously published that SV40 was present in some patients with mesothelioma (reviewed in REF. 35), but the pathogenic implications of this finding are controversial[36–37]. We found no trace of SV40 in biopsy specimens from patients with mesothelioma in Cappadocia, and negative findings were later reported by two other research teams[38,39]. The negative results seemed reliable because in parallel experiments all three research teams had detected SV40 in mesothelioma biopsy specimens from the United States and from Italy (REFS 38,39; P. Rizzo and M.C., unpublished observations). Preparing accurate pedigrees was extremely difficult: there are no official records and the limited information available always lacks the mother's side of the family. For example, four children were indicated as 'sons and daughters of Muhammet' without mentioning the fact that they were from two different mothers. The first two children had both died of mesothelioma, as had their mother. When their father remarried he had two more children who had not developed the disease. The initial analysis had found an incidence of mesothelioma in that family of 50%, but it was 100% on one side of the family and zero on the other. Another major obstacle was the identification of the cause of death, at times reported as 'fate', even in the records of the local health centres. We had to interview hundreds of people and review many clinical records to see how many of those deaths of 'fate' were due to mesothelioma.

The results showed that mesothelioma occurred in certain families but not in others. When members of high-risk families married members of a family with no history of mesothelioma, the descendants developed the disease. The issue of the houses seemed unrelated to the epidemic. Multiple generations of the same family live in the same house, so it was probable that the houses were not to blame, but that the epidemic was genetic, caused by significant inbreeding among the high-risk families of these villages owing to limited contact with people from nearby villages.

We published these results in 2001 (REF. 16). When Y.I.B. read the manuscript he called me and said he did not believe our results. So, I sent him all our data and waited. Less than 6 weeks later he called me and confirmed that, except for a couple of minor mistakes, the pedigrees were correct, and offered to work with me on this project.

Y.I.B. started assembling the pedigrees of the villages of Tuzkoy and of 'old' Sarihidir. Old Sarihidir was a small village of ~300 people in 97 houses who lived in close proximity. This village is located along the Kizilirmak (Red River) and was abandoned in 1960 owing to continuous flooding. The villagers were relocated on the other side of the river. The 'new' Sarihidir has been built with bricks and cement, therefore reducing, but not eliminating, erionite exposure. Some villagers demolished their homes in the old village and used those stones to rebuild part of their new houses. Y.I.B. prepared numerous pedigrees from this village and we met often in Cappadocia to review the data, interview the villagers and examine those with mesothelioma (FIG. 2). A.U.D., a mineralogist, joined our team to investigate whether different compositions of erionite were present in different villages and/or houses, and the possible relationship that this might have with the development of mesothelioma.

Initially it seemed that these pedigrees confirmed the results of our previous work that was based on the pedigrees from Karain and Tuzkoy[16]. Then Y.I.B. produced a pedigree from old Sarihidir showing that mesothelioma had occurred in several people who had married members of a 'mesothelioma family' (FIG. 3; we called this Family 1 because we had to start over). These results argued against my genetic hypothesis and indicated that mesothelioma was caused by erionite exposure, not genetics. We needed the pedigrees of those family members who had married into Family 1. Because of the relocation of the village, many families from old Sarihidir were now scattered around Turkey and Europe. This research was taking more and more of our time and was expensive. So far we had worked during our holidays, using our personal money and time. A.U.D. could no longer sustain the costs of the mineralogical studies with his personal funds. I had similar problems related to the high cost of my travel expenses. Our initial grant applications had been rejected on the basis that there was no published evidence — except for our own — that genetics influenced mineral fibre carcinogenesis. For a few months we did not know how to proceed. Then we were awarded a grant from the American Cancer Society and support from other foundations to continue our studies. However, there were other problems arising. The villagers were unhappy with our paper reporting that genetics was the cause of the epidemic. They felt that this finding marked them and did not obviously help with treatment. And I now had serious doubts about my own genetic hypothesis because of the data on Family 1 and on additional families with similar pedigrees that the research of Y.I.B. had uncovered, including 17 cases of mesothelioma among women who were born outside the villages with high incidence of mesothelioma but had married men in these villages and relocated there. It seemed that when we had finally received a grant for these studies, the entire project was going to collapse.

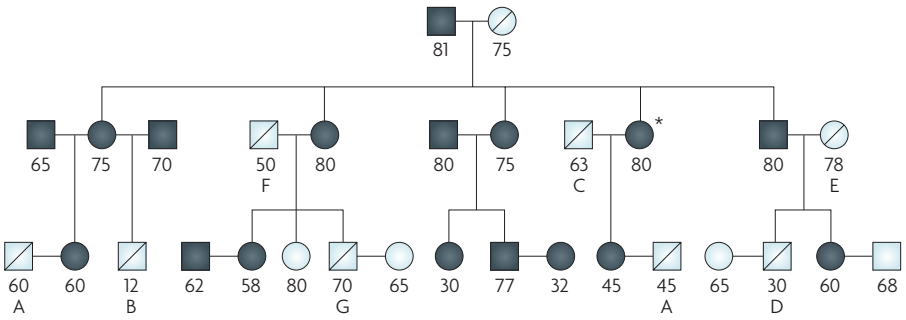

Figure 3 | **Family 1.** A pedigree from old Sarihidir showing a family of 30 members in which 17 died of mesothelioma (shown by the dark symbols), 4 died of other cancers (B of osteosarcoma, D of leukaemia, F of prostate cancer, and G of pancreatic cancer), 5 died of reasons other than cancer, (A because of traffic accidents, C because of an intestinal occlusion, E because of congestive heart failure, and F for unknown reasons) and 4 are alive (shown by the pale symbols). Five mesotheliomas developed in individuals who were born outside this family and who married into this family. They were also from mesothelioma families. A member of this family, indicated by the asterisk, married into a non-mesothelioma family and some of the descendants developed mesothelioma.

However, we continued and found that those individuals who had married into Family 1 (and in families with similar pedigrees) and developed mesothelioma were also from families with a history of developing this disease. At the same time, A.U.D.'s initial mineralogical results suggested that there were no apparent differences between erionite samples from different parts of the world or between samples from different houses or villages in Cappadocia. Furthermore, we found that none of the family members who was born outside Cappadocia had developed mesothelioma.

Together, these results indicated that mesothelioma was caused by the interaction of erionite with an unknown genetic trait. That genetics could influence mineral fibre carcinogenesis was a fascinating hypothesis.

Our most recent studies have confirmed that a genetic predisposition to erionite carcinogenesis is the cause of the mesothelioma epidemic. We found that the levels of erionite in the non-mesothelioma village of Karlik were comparable to those found in the nearby villages with a high incidence of mesothelioma. The same type of erionite, erionite-K, is found in Oregon, Karlik and in old Sarihidir. The chemical analyses indicated that none of the villages had erionite with unusual chemical features. In the same village, no differences in composition or in presence of erionite were found among houses with high, low or no incidence of mesothelioma, and all the houses tested contained erionite. We still need to rule out the possibility that the concentration of erionite in the air could vary among different villages or houses and that this might influence the incidence of mesothelioma. Although significant differences seem unlikely, especially in the same village, we will address this hypothesis experimentally in the near future. Finally, the crystal structure of erionite, obtained with the help of I.S., revealed no differences between erionite samples from Cappadocia and from the United States. In particular, there is no indication of another closely related mineral called offretite.

We found that mesothelioma was prevalent in certain families and absent in others, and that when members of 'mesothelioma families' married into a 'non-mesothelioma family' some of the descendants developed the disease[17]. Unique geographical and cultural characteristics apparently caused the clustering of mesothelioma in these three villages. Our findings do not call into question the large body of literature indicating that erionite is a potent carcinogen that can cause mesothelioma[31]. It is certainly possible that some individuals have or would have developed mesothelioma because of erionite exposure alone. The occurrence of mesothelioma in the few women from nearby villages who moved, as a result of marriage, to the villages with high incidence of mesothelioma supports this interpretation. However, we have recently identified clusters of mesothelioma in families of nearby villages (Y.I.B., S.E. and M.C., unpublished observations) and it is possible that some of these patients are from families who have a genetic predisposition for developing this disease. To date we have not obtained their pedigrees so a final assessment is not currently possible. At the same time, the observation that sporadic mesothelioma is observed among people exposed to asbestos indicates that exposure to certain mineral fibres is sufficient to cause mesothelioma. In conclusion, the data indicate that exposure to erionite causes a higher incidence of mesothelioma in certain families compared with others.

The alternative hypothesis is that the mesothelioma epidemic is not related to erionite at all, but is caused by a founder mutation that has reached a high frequency in this isolated population. There are several lines of evidence that argue against this hypothesis. First, the substantial evidence that erionite is a potent carcinogen[31]. Second, such high frequencies of genetic variation with uniformly high penetrance would be unlikely to show such a limited geographical distribution. The high frequency of disease in certain villages indicates a local high frequency for the genetic variation that increases the risk of mesothelioma, approaching 50% for dominant models and 75% for recessive models. These very high frequencies are much more plausible when penetrance for susceptible individuals is high in the presence of potent carcinogens and low otherwise, than if penetrance is uniformly high, as would be expected for a strictly genetic model of susceptibility (this would be not expected to be restricted to certain villages or households, but to be more widespread). Third, the observation that individuals from high-risk families, who were born and raised outside the three villages, seem to revert to a much lower risk of developing this disease. In fact, 18 descendants from Family 1, aged 25–45 years, were born and raised outside the village of old Sarihidir when the village was abandoned in 1960. No mesotheliomas have developed in this group, but three cases were observed in the same age group among members of Family 1 who were born and raised in old Sarihidir and therefore exposed to erionite. Although the numbers are too small to reach statistical significance and it might take 20 to 40 more years to fully appreciate the significance of this observation, the estimated odds ratio between the two groups is 6.47, and it is consistent with a model of co-carcinogenicity between genetics and erionite. Finally, the observation that the same type of erionite was found in Oregon and in Cappadocia, highlights the potential risk of erionite exposure in the developed world.

Our results indicate that genetic background has a role in determining susceptibility to mineral fibre carcinogenesis, specifically to erionite carcinogenesis in Cappadocia. We propose that the same gene(s) is altered following erionite and asbestos exposure in sporadic malignant mesothelioma and we hope that the isolation of this putative susceptibility gene(s) will lead to new preventive and therapeutic strategies that might benefit

Figure 4 | **The new village of Tuzkoy.** The new village is built with bricks and cement; the old village can be seen in the background. The new village should open in the summer of 2007 or as soon as the roads are covered with asphalt and the sanitation system is completed.

patients in Cappadocia and in the developed world. N. Cox at the University of Chicago, and J.R. Testa at the Fox Chase Cancer Center, have now joined our research team and, owing to a recently awarded National Cancer Institute Programme Project, we will perform genetic linkage analyses to attempt to isolate this putative gene. The presence of genes that predispose to mineral fibre carcinogenesis is supported by recent studies indicating that specific genetic polymorphisms can modify the extent of genetic damage caused by asbestos[40] and that certain genetic alterations seem to increase the susceptibility to asbestos-induced mesotheliomas[41], or are commonly found in mesothelioma samples [2,42,43]. Moreover, villagers with human leukocyte antigen type B41, B58 or DR16 might be at a higher risk of developing mesothelioma[44].

And the villagers?

Given the inevitable, but necessarily, slow progress of our research, we considered various possibilities that would bring immediate help to the villagers.

A new village? I asked whether we could try to convince the government to build new villages for Tuzkoy and Karain — new villages built with bricks and cement that would reduce the exposure to erionite. Y.I.B. had tried in the past to generate economic support to build new villages, but the promises had never materialized. We agreed that there was little to lose in trying again. Y.I.B., S.E., A.U.D. and I addressed the Minister of Health in Ankara to make our case. We explained the problem, and made it clear that this problem was well known to the international scientific community, and that by 'simply' building new villages the Turkish government would be saving the lives of many children. The Turkish Health Minister agreed and said that the government would build a new village in Tuzkoy, and, maybe later, one in Karain. None of us could believe it. We continued to press the case and we found an ally in the Office of the Director of Cancer Control at the Ministry of Health.

In October 2005 when I returned to Cappadocia after an absence of almost a year, Y.I.B. and S.E. told me that they had a surprise for me. When we drove to Tuzkoy I found 96 new houses under construction, and in September 2006 a total of 209 new houses of bricks and cement had been completed on the hill in front of the village of Tuzkoy (FIG. 4). The Turkish government had delivered its promise.

A test for malignant mesothelioma. In October 2005 I co-authored a paper with H.I.P. in which we reported his discovery of a new serum marker for mesothelioma. H.I.P. found that serum levels of osteopontin are increased early in the course of the disease[45]. Robinson in Australia had reported similar results for another serum marker called mesothelin[46]. After consulting with the Turkish Health Authorities, it was decided to prospectively test these serological markers in the villagers (BOX 4). We have tested 80 healthy villagers over the past 6 months. The results have been encouraging — we have already detected two early cases — and the Governor suggested that we offer the test to the entire village. Moreover, the Director for Cancer Control has instructed the local hospitals to provide free radiology screens to verify the diagnosis, and to offer free medical treatment if the diagnosis of mesothelioma is confirmed. For our part, we are paying for the costs of the serological tests, which are carried out by members of my laboratory who fly to the Hacettepe University in Ankara every 3 months.

The villagers have reacted differently to the news. Some (~50%) have expressed the desire to be tested, but others believe that screening is useless until we have some effective therapy to offer. We think that early diagnosis and treatment might benefit patients and at the moment this is all we can offer. We also know that any medical information we discover in Cappadocia — for example, the value of serum levels of mesothelin and osteopontin for early diagnosis, or the isolation of the mesothelioma gene(s) — will probably benefit all patients affected by mesothelioma worldwide.

The new village should open in the summer of 2007. We, the scientists, certainly did not build the village; the Turkish government deserves all the credit for that. But we started the process by bringing a local problem to the attention of the international scientific community first and to the Turkish Government later. We helped to realize something that we considered an impossible dream. And 'we' certainly includes all the agencies and not-for-profit associations that funded this project and made our work possible.

Box 4 | **Ethical issues**

When we found that mesothelioma was more prevalent in certain families than in others we were confronted with the dilemma of whether we should inform the families and, if so, how. Moreover, we needed the blood samples from high-risk mesothelioma family members to try to isolate the mesothelioma susceptibility gene, and the donors would naturally have asked for their results. There was also the possibility that the reasons for these tests would have caused further isolation of these villages, and that in the village high-risk families could be further ostracized. The ethical dilemmas arising from this work have been handled by M.T., the Director of the Office of Cancer Control at the Turkish Ministry of Health. Turkish law requires that, to carry out these studies, we have to report the results to the Office of the Director of Cancer Control, and they will decide what to do with the data. It is they who coordinate the work of the Turkish physicians and nurses who inform the villagers of the nature of the test and collect the serum samples. When the sera are collected we test them at Hacettepe University, Ankara, Turkey, and report the results to M.T. Any decision thereafter, including informing the villagers and coordinating (free) medical screening and therapy if a tumour is detected, is carried out by the Office of the Director of Cancer Control. This approach has worked very well so far.

A further ethical issue concerns how to manage individuals who might have high levels of mesothelin and osteopontin, but who have undetectable tumours. M.T. is coordinating a future chemopreventive clinical trial in villagers thought to be at high risk owing to high levels of these markers. This chemopreventive trial will use ranpirnase (Onconase; Alfacell Corporation), an RNase inhibitor that induces apoptosis in mesothelioma cells in tissue culture[58], and that has proved effective in some patients with mesothelioma with minimal side effects[59].

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Competing interests statement

The authors declare no competing financial interests.

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