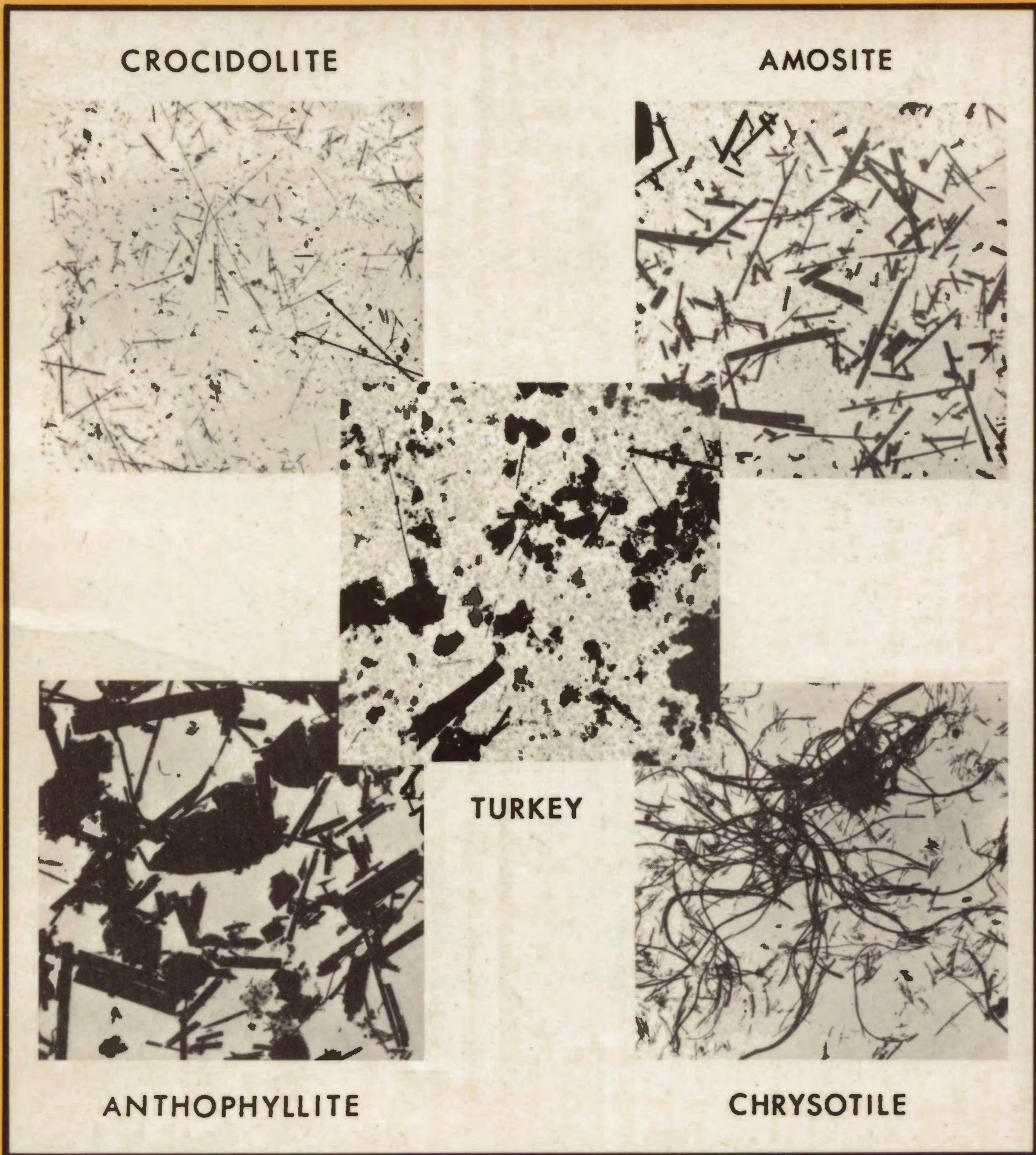

ASBESTOS AND ERIONITE RELATED CHEST DISEASES

Prof.Dr. Y. İzzettin BARIŞ

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To my wife Nural Barış for her encouragement and understanding.

FOREWORD

It gives me great pleasure to write the foreword of this book by Izzet Baris. He has played a major role in our understanding of the association between mineral fibres and the occurence of mesothelioma, a sinister malignant tumour affecting the lining membrane of the chest wall and the abdominal cavity. His description of the situation is so modest that readers of the book will not appreciate the importance of Izzet's personal contribution in these investigations.

Before he became interested in this problem, we had established that this particular tumour appeared to be associated with exposure to the dust from a blue form of asbestos called crocidolite which was mined in South Africa and Western Australia. Further investigations in man had suggested that other forms of asbestos might be involved and our experiments had shown that animals exposed to a variety of mineral fibres could develop these tumours.

The proof that another form of asbestos, "tremolite", can cause these tumours has come partly from Izzet's observations. More significantly, he has shown that the different physical forms of tremolite as recognised by the geologists, cause a sequence of disease dependent on the diameter and length of the ultimate fibre. The coarsest of the fibres being associated with the development of pleural plaques, the medium fibres pulmonary fibrosis and carcinoma of the lung in cigarette smokers; and the extremely fine fibres with the development of mesothelimos of pleura and peritoneum. He has also collaborated in studies in which we have correlated the actual dust recovered from the lungs with these various forms of disease. This has led to very important observations on the significance of retention of specific minerals in the lungs of those exposed to fibrous dusts.

His most significant observations which have shown that a rare mineral fibre formed from volcanic dust, is causing the highest rate of mesothelioma anywhere in the world, has opened up a unique field of study. The significance of his initial observations are universally recognised and we only hope that his return to active research in Turkey will allow us to collaborate in the future investigations which are required to consolidate these studies.

J. Chistopher Wagner

PREFACE

Asbestos has been mined and used since the Stone Age. Its strength, durability and insulation properties have been known for centuries. During the industrial revolution and the Second World War, the utilization of asbestos increased and at present it has numerous uses.

The asbestos textile and insulation industries began after 1935 and asbestosis, along with lung cancer, started to become apparent but its association to mesotheliomas became well known only in the 1960's. In order to prevent occupational exposure to asbestos, its use was severely limited or banned in certain countries, but there are many other countries who still use asbestos and it remains a major threat to health, particularly, among workers in developing countries.

Apart from being an occupational hazzard, there are also some countries where environmental exposure to asbestos is common and is associated with various diseases.

Recent experimental studies have shown that apart from asbestos, some other fibrous minerals including fibrous zeolites, can also cause malignant mesotheliomas.

This book describes and illustrates in some detail asbestos and fibrous zeolite (erionite) related diseases. It is intended primarily as a reference book for clinicians, general practitioners and occupational health physicians who are entrusted with the health care of industrial workers.

The first part of the book reviews the geology, occurences and uses of asbestos, and asbestos related diseases. It further reviews the results of a ten year study of environmental and epidemiological surveys on asbestos pulmonary diseases in nine villages in Central Anatolia, Turkey.

The second part presents information on the geology, occurences and uses of zeolites and reviews erionite induced diseases based on research work carried out in three villages in Cappadocia region of Central Anatolia. To my knowledge, this is the first book that gives information on erionite related diseases.

It is my hope that this book will be helpful in the prevention and early diagnosis of occupational and environmental mineral fiber induced chest diseases.

Y. Izzettin Baris
Ankara, Turkey

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Special credit is due to I. Yigit, former head of Karain Village and E. Tuztaş and their friends for the reports on cases of endemic cancer in the villages which initiated our studies in the zeolite villages; and also to M. Özkan for making available to use the health centres documents.

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I acknowledge with gratitude the contribution of the following persons who made this book possible: Drs. J.C. Wagner, P.C. Elmes, and J.W. Skidmore, MRC Pneumoconiosis Unit, Llandough Hospital, Penarth, Wales, U.K.: F.D. Pooley, Department of Mineral Exploitation, University College of Cardiff, Wales, U.K., for their support and encouragement in conducting the environmental survey of asbestos and zeolite villagers; Dr. S. Alpan, Associate Professor and former Director of the Institute of Mineralogic Research and Exploitation, Ankara, Turkey, and A. Göktepeli also of the same Institute, for allowing us the use of all facilities of the institute for the conduct of mineralogical and geological studies in the villages: Dr. H. Acan, former General Director for National Association Against Tuberculosis, Ministry of Health and Social Affairs, Ankara, Turkey and his staff, for the provision of the microfilms of the asbestos and zeolite villages.

I would also like to thank, Dr.J. Higgins, former Director of IARC and his colleagues, Drs. R. Saracci and L. Simonato for supporting the epidemiological studies in the zeolite villages: Drs. P. Sebastien, J. Bignon and their colleagures of Laboratoire d'Etudes des Particulas Inhalees and Centre Hospitalier Intercommunal, Paris, France, for their contribution in mineralogical studies in lung tissues and ferruginous bodies in the sputum.

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CONTENTS

PART II ZEOLITES

PART I

ASBESTOS

A. DEFINITION, GEOLOGY, USES AND TYPES OF EXPOSURE.

B. ASBESTOS - RELATED DISEASES

- MALIGNANT MESOTHELIOMA
- BENIGN MESOTHELIOMA
- BRONCHIAL CARCINOMA
- GASTROINTESTINAL CARCINOMA
- OTHER ORGAN CARCINOMAS
- ASBESTOSIS
- IMMUNOLOGIC CHANGES
- PLEURAL EFFUSIONS
- PLEURAL PLAQUES
- PLEURAL THICKENING

C. ASBESTOS - RELATED DISEASES IN TURKEY

DEFINITION, GEOLOGY, USES AND TYPES OF EXPOSURE

Asbestos is a term applied to six naturally occuring SILICATE MINERALS exploited commercially for their physical properties which are in part derived from their FIBROUS STRUCTURE. These minerals are the SERPENTINE MINERAL and the AMPHIBOLE MINERALS.

The word "Asbestos" is derived from the Greek word, "Asbestinon" meaning "Incombustible". Some of the European countries use "Amiante" instead of asbestos which orginates from the Latin word "Amiantos" meaning" Spotfree".

The discovery, through archeological research of asbestos in stone age pottery and sheds, demonstrates how far back mankind's contact with this material stretches. It is cheap and easily obtained. Furthermore it is resistant to external agents, heat, acids and friction, and in addition it is easy to process. All these properties have made it useful to man for many centuries.

The different types of asbestos are classified according to whether the fibers are curved or straight, as in the following table:

Table 1: Varieties of Asbestos

1. Serpentine: Curved Fibers
   Chrysotile: White Fibers
2. Amphibole: Straight Fibers
   Crocidolite (Riebeckite Asbestos): Blue Asbestos
   Amosite: (Grunerite Asbestos): Brown Asbestos
   Anthophyllite Asbestos
   Tremolite Asbestos
   Actinolite Asbestos

Chrysotile asbestos is produced mainly in Canada and also in USSR, South Africa, USA, Italy and Cyprus. It constitutes 95 percent of commercially used asbestos. Crocidolite asbestos is produced in South Africa and Western Australia. Anthophyllite asbestos is extracted in Finland, Bulgaria, and USSR. Brown asbestos or amosite asbestos deposits are widespread in South Africa. Tremolite asbestos is found throughout the world but is of little economic value.

The main uses of the various types of asbestos under discussion are listed in Table 2.

Table 2: Uses of asbestos

Type	Uses
CHRYSOTILE	
Short Fibers	Asbestos cement pipes, floor tiles, brake shoes, etc.
Long Fibers	Textile industry
CROCIDOLITE	Battery cases, acid resistant fillers, asbestos cement sheets and pressure pipes. Spraying on bulk-heads and underdeck on ships.
AMOSITE	
Short Fibers	Asbestos cement, filler in plastic, etc.
Long Fibers	Thermal insulations
ANTHOPHYLLITE	Filler in asbestos cement, etc.

The main uses of asbestos and possible health effects are shown in Table 3.

Table 3: Uses of asbestos and possible effects on health

Work Place	Type of Asbestos Used	Health Hazards
Ship yards	Crocidolite, Amosite and Chrysotile	Lung cancer Mesothelioma Asbestosis Pleural changes
Insulation	Amosite and Chrysotile	Mesothelioma Lung cancer Pleural changes Asbestosis
Automobiles:	Chrysotile	Asbestosis
Building Industry:	Chrysotile mainly	

In some cases physicians may not be aware of their patients' occupational asbestos exposure and the possible consequent health risk. The following Tables (4 and 5) illustrate the major uses of asbestos and the occupations involved.

Table 4: Uses of Asbestos

Heat Insulation:

Boiler and pipe packing, pipe covering, insulation blocks and board, insulation jackets, spray on structural heat insulation, ironing board covers, pot holders, table pads, stove mats, gloves lining, auto mufflers, firewall and hood lining.

Electrical:

Insulating tape, transformers,condensors, cables, conduits, electrical wire insulation, spark plugs, switch boxes, circuit brakers.

Friction Materials:

Gaskets, clutch plates, brake lining, bearing packings, seals, conveyor belting.

Building Materials:

Sheets for interior and exterior walls; pipes for gas, water and sewage; reinforced asphalt, vinyl floor tiles, linoleum, panels, partitions, clapboard, asphalt siding and shingles, putties, ceiling board, millboard, stucco, plaster, artifical wood, sound proofing, facing of acoustic tiles, cement, paint, roof covering, caulking, asbestos felt.

Miscellaneous:

Cloth, sheets, blankets, curtains, drapes, rugs, yarns, cords, ropes, twines, ribbon, artificial snow, filler in rubber goods, welding electrodes, filter for fruit juice, medicine and beer processing; cigarette filters, gas mask filters, filter cloths, filter pads, filter paper, catalyst supports for sulfuric acid production and waterproof bearing and packings, cardboard, paper boat hulls, airplane wings, wicks for lamps and burners, prison cell padding, fire hose, mail bags, motion picture screens, frying pan handles, rocket re-entry nosecones, plastics, piano padding, military helmet liners, asbestos asphalt, asbestos reinforced hard standing, parking lots, cartridges, automobile undercoating, fire-proof safety clothing, life jackets, molds, clay for pottery and sculpture.

Table 5: Exposure to asbestos

Occupational

(Regular) Asbestos rock mining, loading, trucking, crushing and milling: asbestos carding, spinning and weaving: electrical appliance and wire manufacturing, masons, carpenters, absestos tube wrappers (laggers), asbestos cork insulation workers, construction workers, laborers, sheets metal and heating equipment workers, building material manufacturing, filtering materials manufacturing, processing and molding of asbestos products, rod manufacturers, munitions manufacture, asbestos cement and plaster making, asbestos asphalt making, putty manufacturing, boiler makers, plumbers, steam fitters, cardboard manufacturing, gasket, clutch plate, and brake-lining manufacturing, asbestos felt insulation, asbestos sound insulation workers, asbestos insulation mixers and sprayers, pipe coverers, automobile makers, garage and service station attendants, ship builders and breakers.

(Irregular) Repairmen, maintenance men, engineers, mechanics, laboratory technicians, office workers, medical personnel, shipping personnel, sailors, longshoremen and dock workers, railroad workers, laundry and dry cleaning personnel.

Nonoccupational: Residents near asbestos processing and textile mills; personnel living and working near roads on which asbestos is trucked; inhibitants of houses with asbestos insulation; people living in houses with asbestos workers.

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ASBESTOS RELATED DISEASES

Below are the diseases encountered in people who are exposed to asbestos, through occupational, environmental or indirect means.

Table 6: Asbestos Related Disease

I. Neoplastic Disease
   1. Mesotheliomas: Malignant.
   2. Carcinoma of the bronchus
   3. Extrapulmonary carcinomas
      a. Gastrointestinal carcinomas
      b. Other organ carcinomas

II. Asbestosis

III. Immunologic Changes

IV. Pleural Reactions
   1. Pleural effusion
   2. Pleural plaques
   3. Pleural thickening

On the hands of labourers working in asbestos quarries and mills, one can identify warts where the mineral has embedded itself as well as Dupuytren's contracture connected with the use of shovels.

MALIGNANT MESOTHELIOMA

Diffuse malignant mesothelioma is a tumour which arises from the mesothelial cells that line the body cavities. It can occur in any of the body cavities, most frequently in the pleura or peritoneum, but also in the pericardium and tunica vaginalis of the testis.

Hillerdal (54) reviewed 4,710 published cases of malignant mesothelioma in 1982. The areas of involvement were 4181 pleural, 454 peritoneal, 33 pericardial, 9 tunica vaginalis of testis and 3 of undefined site.

Malignant mesotheliomas are comparatively rare. In the general population, the incidence of the disease is approximately 1-2.2 per million per year, (65, 73, 115) and in a community which is not exposed to asbestos, the distribution between sexes is almost equal. In industrialized countries it is two to five times higher (29, 73). In certain areas such as shipyard communities and in workers in asbestos factories, it is very high (20-fold or more). In autopsy material the frequency is from 0.02 to 0.7% (59). The frequency is however much higher in asbestos workers. In a study of over 300 autopsies in asbestos workers, 3 percent had mesotheliomas, a 300-fold increase in incidence over the general population (106).

Although the neoplasms of serous cavities were described a long time ago, their introduction in a definite form into medical literature only took place in the second half of this century. Initially these tumours were not recognized as a separate entity.

It was thought that they were the result of chronic irritation from pleural or peritoneal effusion or secondaries. Klemperer and Robin (58) suggested that these tumours were real mesothelial neoplasms. Lynch and Smith (69) first suggested the possible relation between lung tumours and asbestos exposure. In 1953 Weiss (128) reported that asbestos may be responsible in the pathogenesis of mesothelioma. Stout (113) classified the mesotheliomas in 1951. Wagner, Sleggs and Marchand (118) described 33 cases of malignant pleural mesothelioma which had developed through the environmental effects of asbestos in the Republic of South Africa's north-west Cape region in 1960. Attention was drawn to the mesothelioma-asbestos link after the appearance of this report. A dispute arose between those who accepted the asbestos-mesothelioma connection and those who did not. However, taking into consideration the environment of the patients, the protracted course of the disease and the tumour's macroscopic and microscopic appearances, it was eventually accepted that mesotheliomas are primary serous membrane tumours and that in their pathogenesis there had to be a link with asbestos.

ETIOLOGY

Asbestos: Clinical, epidemiological and pathological surveys and in vivo and in vitro experimental work demonstrate that asbestos is responsible for the etiology of mesothelioma.

Epidemiological and pathological studies carried out in South Africa (52, 118, 124), the United Kingdom (38, 50, 81-83), Canada (38, 73, 74), USA (39, 105, 108), France (35), West Germany (17) and Australia (76, 77) have emphasized that 70 to 85 percent of mesothelioma patients have been exposed to asbestos through occupational, environmental or other means.

Gilson (48), demonstrated the connection between the inception of the asbestos industry, its expansion and the occurence of lung diseases. Modern asbestos production began in 1878 and by 1970 had reached great proportions. At the beginning,preventive measures to control dust were not taken and by the 1900's a high incidence of lung fibrosis (asbestosis) had occured. With the introduction of preventive measures from 1935 onwards this gradually receded. For a time, since labourers died at an early age because of lung fibrosis, the neoplastic effect of asbestos was camouflaged. The asbestos textile and insulation industries began after 1935 and asbestosis, along with lung cancer, started to become apparent. From the 1950's onwards active measures were taken against excessive inhalation of asbestos and mesotheliomas which may be due, probably, to inhalation of reduced quantities of asbestosis fibre began to appear.

The demonstration of asbestos fibres or asbestos particles in the neoplastic tissue was further strong evidence that asbestos has a role in the development of mesotheliomas.

Histopathologic studies in this area were at first not conclusive. However, later on light microscopic and electron microscopic (EM) examinations of the neoplastic tissues achieved positive results. Turaif and colleagues (117),found asbestos fibres in the deeper layers of the tumour and in the adjacent pleural tissue. Ashcroft and Heppleston (8), reported that they found $154\text{-}684 \times 10^6$ asbestos fibers in 1 gram of dry lung tissue with EM examination. Pooley (90), found more asbestos fibres in the lung tissues of 120 persons with mesothelioma when he compared them with 135 controls.

Through experimental work, the link between asbestos and mesothelioma has been revealed. Wagner and colleagues (119) by injecting rats intrapleurally amosite, chrysotile and crocidolite asbestos, induced mesothelioma, sarcoma and other tumours.

Stanton and co-workers (112),using various types of asbestos and glass fiber, silicate and metal particles with a different method have induced pleural mesotheliomas in rats. Experimental researchers have indicated that the fibre diameter, length and shape may be important. The size and shape of the fibres influence the incidence of tumours; fibres less than 0.25 micron in diameter and whose length is more than 8 micron, that is, thin and long fibers are more active in producing tumours. The short and thick fibres are less oncogenic. This is largely because they are easily phagocytosed. Stanton and colleagues (112),showed that fibres of the other materials, including glass, could induce mesotheliomas, but only when the diameter was the same order as that of asbestos, when measured by light microscopy and as long as they are durable in lung tissue.

Shabad et al. (103), reported that when Russian chrysotile was injected intrapleurally 3 times into 67 rats, 31 developed mesothelioma within 2 years. They also demonstrated mesothelial cell proliferation and adenomatous changes in the animals and labelled these changes as premesothelial changes.

Experimental research carried out on animals is difficult and lengthy. Impetus has thus recently been given to simpler and quicker result-producing in vitro studies (13). The toxic and carcinogenic effects of asbestos fibres have been shown in mesothelial tissue culture, mononuclear phagocytes and erythrocytes (56). Brown and Chamberlain (20),showed that fibres of less than 1.5 microns in diameter and more than 8 microns in length were more toxic to the cells. Davies (32),noted that release of certain enzymes such as lactic dehydrogenease and beta-glucoridase, by the peritoneal macrophage following contact with the mineral fibres demonstrates the fibrogenic character of the fibres in the tissues.

Is there any relation between the type of asbestos and the development of mesothelioma? In the region of the blue asbestos mine in the north-west Cape region of South Africa, the incidence of pleural mesothelioma was found to be higher as compared to the Transvaal region where amosite asbestos is found. This was the reason why it was felt in the past that crocidolite type of asbestos is responsible for mesothelioma. However mesothelioma was reported in the workers who were exposed to amosite type asbestos in the USA (107). Mesothelioma was not reported in Finland where anthophyllite type of asbestos is found in abundance (53).

The interval between exposure to asbestos and the development of tumour is a long one. It was precisely for this reason that for many years the link between mesothelioma and asbestos went unnoticed. From various surveys it is understood that mesothelioma manifests itself at the earliest 3.5 years and at the latest 73 years but on average 37.0-40 years after exposure to asbestos (37, 54).

We cannot explain all cases of mesothelioma purely on the basis of exposure to asbestos. There are many other factors which need to be considered. Pathogenic activities of certain types of asbestos seem to be different. The dust concentration, the duration of exposure, additional role of milling of asbestos, the person's cellular or humoral immunity, and exposure at different ages, all play a role in the production of asbestos related disease.

Sometimes mesothelioma occur with exposure to only a small dose of asbestos over a short period. In fact, a 21-year-old patient of Wagner and his colleagues (118),informed them that in his childhood he had spent only a short time in an asbestos district. One-third of Elmes's cases were in contact with negligible amounts of asbestos (37). A patient of Demy and Adler (36) was exposed to asbestos for only a 6 month period. In a case reported by Ṅewhouse (81), asbestos was inhaled for only two months. On the other hand, the same researcher in another paper claims that the frequency of incidence of mesothelioma is proportional to the asbestos fibres inhaled during a period of time (82).

Besides occupational exposure to asbestos, domestic exposure of household contacts may also occur from dusts brought home on workers' shoes, hair, equipment, etc. Other domestic exposures, also widespread, are para-occupational exposures from household repairs and do-it-yourself construction using asbestos-containing materials, such as asbestos cement sheets, plaster fillers and wall-joining compounds, furnace and heating equipment cements and other repair materials (84).

House contact with asbestos is associated with increased risk for mesothelioma. Mesotheliomas have occurred in household contacts and in non-occupationally exposed persons living in the neighbourhood of industrial sources of asbestos (81, 84, 118).

Mesothelioma has been reported in children and there has been no apparent history of asbestos exposure either directly or indirectly in the majority of the cases (123). There is also no specific geographical distribution. Mesothelioma in children constitutes only 3% of reported cases. The time required for the development of the disease in children is from between 9 months to 14 years. Wasserman and colleagues (123), have suggested that the disease in these children is due to transplacental transfer of asbestos from the mother. According to these authors, insufficient immunological protective mechanism in early life is the reason for the earlier development of mesothelioma. On the other hand, Pontefract and Cunningham (89), have demonstrated asbestos in the foetus after I.V. injection of asbestos in experimental animals which tends to confirm the possible trans-placental passage of asbestos fiber from the mother.

Does asbestos only have fibrogenic and oncogenic effect when taken through the respiratory system? There are lots of asbestos fibers in the environment, some of which are easily ingested through food and drink.

E-M-studies carried out on municipal water in Canada and U.S.A. detected 1-173 million asbestos fibers per liter (28). The contamination of water by asbestos may take place either by dumping of mineral remains into the water or from the asbestos made pipes. Biles and Emerson (14), found asbestos fibers in beer. Nicholson and his colleagues (85), demonstrated the presence of asbestos in some parenteral ɿedicines such as sodium ampicillin, neomycin, and tetracycline HCL. Other researc rs have demonstrated that asbestos passes through the digestive tract. Westlake et al. (129), reported that the fiber passes through the colonic mucosa. Carter and Taylor (22), found asbestos in the liver, lungs and small intestines of people who ingested high amounts of amphibole asbestos. Telishi and Rubenstone (114), identified asbestos bodies in the gastric mucosa of an asbestos worker who had asbestosis together with bronchial carcinoma, gastric carcinoma as well as bronchial adenoma.

Epidemiological studies carried out on asbestos workers revealed that neoplasms of the digestive system, such as gastric and colonic carcinomas were 2-3 times more common than in control groups (82, 102, 106).

The evidence above, suggests the oncogenic nature of asbestos on the digestive system also. However, experimental studies, other than those of Gibel et.al. (47), with rats fed on asbestos, demonstrate that tumours do not develop at a significant rate.

In their discussion of the carcinogenic effect of asbestos on the digestive tract, Bignon and Bader (15), suggested that asbestos in beverages may be responsible for liver cancer in alcoholics. They suggested that there should be prevention of the contamination of asbestos in food and drinks and that a lot more research work should be carried out on the relationship of asbestos exposure and the development of gastrointestinal cancer.

It is not always possible to explain all mesotheliomas on the basis of asbestos inhalation. As we commented earlier, 15-30% of cases have not been exposed to asbestos. In a study of patients in Finland, between 1953-1969, Nurminen (86), observed that in 11% of cases, there was definite exposure; in 34.2%, there was probable exposure; in 40.2%, exposure could not have been possible and the remaining 14.6% were undecided. He indicated that other etiological factors may be present and this has been confirmed by other researchers.

Asbestiform Minerals: Asbestiform mineral means, crystal habit of a mineral resulting in thin, hairline fibers on a microscopic or submicroscopic level, resembling asbestos.

A number of fibrous minerals other than the asbestos varieties exist in nature. Some of these occur as natural contaminants of rocks and ores and are released during mining, milling or processing. As an example, talc may be contaminated with asbestiform (fibrous) tremolite, anthophyllite and chrysotile. Excess deaths due to lung carcinoma, pleural fibrosarcoma, peritoneal mesothelioma, gastrointestinal tract cancer and other cancers have been recorded (57).

Some asbestiform minerals and their relation to certain asbestos types are shown in Table 7.

Fibrous Clays: Fibrous clay minerals such as sepiolite and palygorskite (attapulgite) are mostly mined to a significant extent in the U.S.A. and Spain. The main uses of fibrous clay are cat litter, oil absorbents in factories and vehicle maintenance depots.

Table 7: List of rock-forming minerals which may form fibers and their relationship to asbestos.

Asbestos type	Asbestiform-related Mineral
Actinolite - tremolite	Ferroactinolite
	Garnierite
	Hexagonite
	Richterite
	Tirodite
Anthophyllite	Ferroanthophyllite
	Ferrogedrite
	Gedrite
Crocidolite	Crossite
	Glaucophane
	Magnesioriebeckite
	Riebeckite
Amosite	Cummingtonite
	Grunerite
	Kufferite
	Montasite

Pott et al. (92), produced mesotheliomas with a specimen of palygorskite. Wagner and co-workers (119), produced some mesotheliomas in animals only by intrapleural implantations, but not inhalation.

Radiological studies showed only minor abnormalities among the sepiolite workers (12).

Man-made Mineral Fibers: Man-made mineral fibers (MMF), include different inorganic synthetic wool products such as slag wool, glass wool, and rock wool. The production of MMF has increased enormously in recent times, since it has replaced asbestos as thermal and acoustic insulation material and as filament products used for textile manufacturing and for the reinforcement of plastic materials.

Animal experiments have clearly shown that a carcinogenic effect can be induced by direct intrapleural administration of MMMF (91, 112). On the other hand, no carcinogenic effect has been detected in inhalation studies (51, 119).

Epidemiological and mortality studies in relation to lung fibrosis and malignancy in MMMF workers in U.S.A. and Europe did not reveal any significant pulmonary radiologic and/or physiologic abnormalities when compared to control groups (40, 79, 101).

All the available evidence suggests that MMMF is not a potential hazard to man. Despite this, however, the production and use of microfibers should be strictly controlled.

Zeolites: Zeolites are a complex group of silicates formed by metamorphosis in deposits of volcanic ash. There are more than 30 naturally occuring zeolites and they tend to occur in mixed deposits contaminated with other volcanic minerals and glasses. Most of the natural zeolites are non-fibrous, but two of them, namely, erionite and mordenite have fibrous forms.

Cappadocia region of Central Anatolia is rich in zeolites. Our environmental studies in the Cappadocia area showed that there is a high prevalence of fiber-related chest diseases in Karain and Tuzköy villages. Fibrous zeolite (Erionite) has been recovered from the lung samples and sputa of the patients. The effect of erionite exposure has been studied in animals and showed a high carcinogenic potential when injected intrapleurally and on inhalation. These findings have been supported by in vitro studies. This subject will be discussed at length later.

Other Agents: Mesotheliomas have been developed in experimental animals with plutonium, beryllium, and other carcinogenic materials (9, 49, 100). However, it is very difficult to demonstrate this in human beings. It has been reported that the accidental contamination of the peritoneum with thorotrast, while cholangiography was being done during surgery, was the cause of peritoneal mesothelioma 30 years later (75).

Chabot and co-workers (23), induced mesothelioma by MC29 avian leucosis virus in the peritoneal and pericardial sacs of chicks.

Chretien and co-workers (26), reported 4 cases of pleural mesothelioma in patients who underwent the old collapse therapy for pulmonary tuberculosis. Roviaro and colleagues (98), reported 3 cases of mesothelioma with calcific pleural tuberculosis and thought that chronic pleural stimulation could be the initiative factor.

Tuman, et al. (116), reported that isoniazide taken pre-natally causes mesothelioma in the child.

In five patients living in a rural area of India, Das and co-workers (31) diagnosed mesothelioma, without obvious asbestos exposure. Although they suggested that sugar cane could be the possible factor, this was not accepted.

The etiology of mesothelioma may be summarized as follows:

1. *Asbestos: Mostly crocidolite and amosite type. There is evidence from radiological screening, epidemiological surveys, mortality studies and case control studies together with in vivo and in vitro data.*
2. *Asbestiform minerals: Both experimental studies and environmental survey show that these minerals may cause mesothelioma.*

3. *Clay minerals: Mesothelioma has been seen only in experimental work.*
4. *Zeolite: Based on epidemiological, in vivo and in vitro studies, fibrous type zeolite (erionite) is the most potent carcinogenic and fibrogenic fibrous mineral*
5. *Man-Made Mineral Fibers: Mesothelioma has been seen only experimentally, by the injection or instillation of glass fibers into pleural or peritoneal cavities. Inhalation experiments and epidemiological studies with mortality surveys in man have been negative.*
6. *Exposure to thorotrast, radiation, plutonium, beryllium and other carcinogenic materials: There are only occasional case reports.*
7. *MC 29 Avian Virus: Carcinogenic only in chicks.*
8. *Chronic inflamation and chronic irritation of pleura by calcification: There are some case reports.*
9. *Miscellaneous: Such as INH taken prenatally.*

The most common fibrous mineral producing mesothelioma is asbestos, but the most potent is erionite. Fig. I shows the main types of asbestos compared to erionite fiber from Turkey.

PATHOLOGY

The mesothelial cell is pluripotential owing to its origin from mesoderm. It presents a variety of histological appearances. Various irritants can cause metaplastic changes of the epithelial type, squamous metaplasia or of connective tissue types. Such changes may easily be mistaken for malignancy. The mesothelial cell can phagocytose and produce collagen and can desquamate and then become rounded. These properties can explain some of the histological diversities, as well as its behavior.

Gross Pathology: Macroscopic appearances of these tumours are more characteristic from the histological view point. The disease may begin in the parietal or visceral pleura. However, in the early stages the parietal pleura is mostly involved. The tumour is usually hard, white or yellowish-grey in colour, fills the pleural cavity and envelopes the viscera. As the costal and visceral layers fuse, any pleural fluid will diminish. The progression is usually slow and in the later stages invasion of contiguous tissues takes place. The affected hemithorax will be fixed and due to the diffuse fibrous tissue there will be shrinkage of the ipsilateral hemithorax. Multiple white, or gray granules and nodules appear on both visceral and parietal pleura.

In advanced cases, the diaphragm, pericardium, heart, contralateral pleura, mediastinum and liver may be involved. Hematogenously disseminated metastases are present in 50 percent of patients. Death generally results from complications arising from the local disease. In one study of 115 cases, it was found that epithelial types behaved more as carcinomas and spread by direct extension into tissues and regional lymph nodes (4). These tumours showed some response to radiotherapy. In contrast, the un-

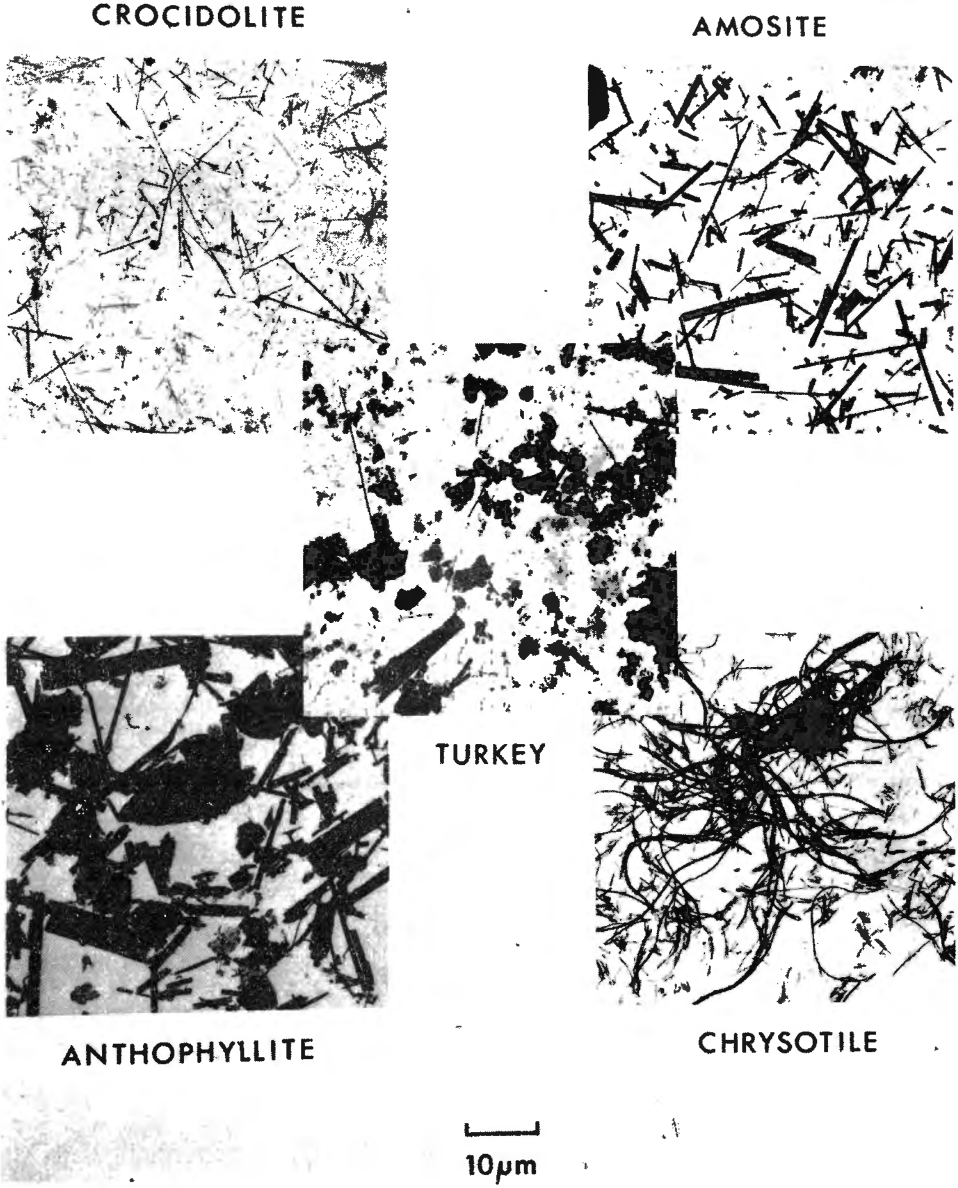

Figure 1. Electron micrographs of dispersed samples of the main types of asbestos fibres and Turkish Erionite fibres.

differentiated sarcomas had shorter survival time and more frequent distant metastases. It has been claimed that patients with a lymphocytic infiltrate in the tumour may survive longer than those without (66).

Macroscopic diagnosis of peritoneal mesothelioma is very difficult. Widespread nodules are seen on the surface of the peritoneum in addition to fluid accumulation. There are usually fibrous adhesions and the intestines may be mottled together to give an impression of a mass. Metastases are found in the liver, other abdominal organs and the abdominal wall.

Histology: There are three types of malignant mesothelioma. Epithelial, the mesenchymatous (Sarcomatous or fibromatous) and the mixed types (25, 55). A tubulopapillary pattern is that which is most frequently encountered in the epithelial form. It is characterized by uniform cuboidal or polygonal cells arranged in a complex papillary pattern or in a single layer around slit-like spaces, an appearance not often seen in secondary adenocarcinoma. In the sarcomatous variety, the epithelial elements are scanty and the main cell type is spindle-shaped and there may be an abundance of collagen. The mixed form reveals both epithelial and sarcomatous forms.

The histological subtypes of mesothelioma was tabulated from the 4,710 reported cases by Hillerdal (54). Table 8 shows the distribution.

Table 8: Histological subtypes of mesothelioma as found in published reports

	Pleura	Peritoneum	Pericardium
Epithelial	412 (50%)	45	4
Mixed	283 (34%)	23	13
Sarcomatous	134 (16%)	7	2

Diagnosis of mesothelioma from needle biopsy specimens sometimes creates diagnostic difficulties, particularly in distinguishing mesothelioma from reactive mesothelial hyperplasia or secondary adenocarcinoma. In such cases the cell shape is of importance and cuboidal cells are suggestive of adenocarcinoma. Mesothelial hyperplasia associated with effusions may be more difficult, but the presence of a papillary pattern is a compelling pointer to a malignant mesothelioma. Yet, even in the best hands, needle biopsy alone is likely to reveal the diagnosis in only 40-60% of cases (127).

Separation of several pleural lesions is sometimes difficult clinically. A combination of biopsy and cytological examination of fluid may yield diagnosis of malignant mesothelioma during life.

Kwee and co-workers (72), suggested certain diagnostic methods for the diagnosis of mesothelioma. The authors sought to distinguish between malignant diffuse mesothelioma, reactive mesothelial hyperplasia and metastatic adenocarcinoma, using histochemical stains, immunostaining for carcinoembryonic antigen (CEA), and morphometry by measurement of mean nuclear area. Hyaluronic acid activity that was diminished or suppressed with hyaluronidase digestion was found in 49% of cases of malignant mesothelioma, but not in cases of pleural metastases or mesothelial hyperplasia. Positive staining with PAS after diastase was present in 60% of cases of pleural secondaries, but not in cases of benign or malignant mesothelial lesions. Sixty-four percent of cases of pleural metastases were CEA-positive, but no cases of mesothelial neoplasm or proliferation were positive. Mean nuclear area was remarkably effective in separating benign mesothelial proliferation from pleural metastasis or mesothelioma: The mean nuclear area for benign lesions was 23.7 ± 8 $m\mu^2$ compared to a value of greater than 55 $m\mu^2$ for malignant mesothelioma or secondary carcinoma. However, malignant mesothelioma and metastatic carcinoma had virtually identical mean nuclear areas. In summary, 88% of metastatic carcinomas could be distinguished from mesotheliomas by the combined used of diastase - PAS and CEA stains. All malignant pleural lesions could be separated from benign mesothelial hyperplasia by quantitative studies of mean nuclear diameter.

Electron microscopy can also be utilized to distinguish between metastatic adenocarcinoma and epithelial mesothelioma with variable degrees of certainty, depending upon the fixation technique and the experience of the electron microscopist. The separation of mesothelial hyperplasia from mesothelioma can be very difficult with routine light microscopy. E.M. examination, of small biopsy material is the most beneficial method of diagnosis (34, 41, 67).

Cytology: Examination of pleural fluid or ascites for mesothelioma is extremely difficult largely because of the problem of differentiation of neoplastic from reactive cells. One diagnostic difficulty results from the behaviour of normal serosal mesothelial cells when exposed to certain stimuli, such as infarction. The simple layer of flattened cells become rounded and float off into the exudate and papillary or pseudoacinar structures may be formed.

In cytological preparations of cell deposits from serous effusions, the picture may be quite characteristic. "Cell Balls" are often present, but these may also be present in many cases of adenocarcinoma and even in benign mesothelial proliferations. From any of these causes the cell aggragates may be hollow (pseudoacini) or solid with a collagenous core. Adenocarcinoma cell clusters often include large degenerative vacuoles, not related to mucus secretion. Benign cell clusters and those of mesothelioma do not show this feature though they may contain lipid granules. Malignant cells derived from sarcoma-like form of mesothelioma are rare (18, 61).

When the diagnosis is between mesothelioma and benign mesothelial cell proliferation, karyotype analysis of cells is useful. The presence of a clone of cells with an abnormal karyotype has been reported only from malignant effusion (70).

Lastly, immunochemical staining with monoclonal antibodies has provided a new progressive advance in cytological diagnosis, by failure to react with anticarcinoembryonic-antigen, but give positive staining with certain anti-epithelial antibodies (122).

In summary, for the accurate diagnosis of mesothelioma, in addition to the environmental history, clinical and radiological data, and the macroscopic appearances of tumour during operation or autopsy, the following are necessary:

Light Microscopic Picture: Tubulo-papillary pattern for the epithelial form. Fibromatous form is characterised by scanty epithelial elements, but the main cell type is spindle-shape with a lot of collagen.

Sarcoma-like form has sheets of polygonal cells containing large vesicular nuclei with one or more prominent nucleoli.

Histochemical Stains: PAS stain for neutral mucin, alcian blue or similar stains for hyaluronic acid for separating mesotheliomas from metastatic adenocarcinoma.

Immunostaining or CEA as a further discriminatory method because mesotheliomas are CEA negative.

Detection of anti-epithelial antibodies, notably those against "epithelial membrane antigen".

Morphometric Study: Measurement of mean nuclear area for separating malignant pleural lesions from benign lesions.

Electron Microscopic Study: For ultrastructural evaluation. In cases of doubt, the opinion of a very experienced histopathologist should be sought.

Cytological Study: Including karyotype analysis and immunochemical staining.

CLINICAL MANIFESTATIONS

The clinical manifestations of malignant mesothelioma were collected from Elmes and Simpson's 327 cases, Hillerdal's 4,710 cases and Law, Hodson and Turner-Warwick's 140 cases (37, 54, 64).

Age and sex: In Elmes and Simpson's cases, there were 268 males, 59 females, their ages ranging between 29 to 88 years and mean age was 59. In Hillerdal's series, pleural mesothelioma was found mainly in males (3.6 to 1) and were commonly diagnosed at ages 50-70 years. There were 115 males and 25 females, aged 33-76 years, with a mean age of 58 years. In Law, Hodson and Turner-Warwick's series, two-thirds of the patients were between the ages of 40-70 years.

Symptoms: The onset is most often insidious. The most common initial symptoms are malaise, general fatiguability, anorexia and loss of weight. Later on chest pain, dyspnea and rarely fever and cough appear.

The most prominent complaints of patients are chest pain and shortness of breath. The pain initially starts as a fullness, heaviness or numbness in the chest and the severity increases with time. The chest pain is usually non-pleuritic and is frequently referred to the upper abdomen or shoulder because of diaphragmatic involvement.

At the beginning, dyspnea occurs on exertion and is mostly related to pleural effusion which can be massive and associated with mediastinal shift. It is rapidly relieved by thoracocentesis but, it recurs within a short period. In some cases, asbestosis and encased lung may play a role in the dyspnea. Most patients have symptoms for several months before they see a doctor.

Some patients have irregular episodes of low-grade fever or intermittent fever and sweating (64).

Rarely hypoglycemic features such as syncopal attacks, manic reactions and convulsions may occur, but hypoglycemia and pulmonary osteoarthropathy are much more common with benign mesothelioma.

In patients with peritoneal mesotheliomas, the most frequently encountered symptoms are, abdominal distention, generalized pain, constipation and rarely diarrhea associated with anorexia and weight loss (5, 78).

Clinical Signs: The most frequently encountered physical findings in patients with pleural mesothelioma are as follows:

1. Pleural effusion: Usually massive and characteristically accumulates rapidly after pleural tapping.
2. The mediastinum is pushed to the opposite side. In the late stages, the tumour encases the ipsilateral lung and produces a mediastinal shift to the side of effusion resulting in a loculated effusion. This is quite characteristic for mesothelioma.
3. Cyanosis, tachypnea, and tachycardia.
4. Skin deposits of tumour in previous aspiration sites, thoracoscopy or thoracotomy scars.
5. Evidence of tumour extension: On chest wall, pericardium, mediastinum, and liver.
6. Frozen chest and droping of shoulder on affected side and scoliosis because of extensive involvement of costal pleura.

Unusual presentation such as neural involvement, *Horner's syndrome* (10), *sympathetic nerve invasion* (111), *recurrent laryngeal nerve paralysis* (93), *invasion of spinal canal with acute paraplegia* have been described. *Esophageal compression* with *dysphagia*, *obstruction of superior vena cava, hypertrophic osteoarthropathy,* as well as *bilateral malignant lymphangitis* (110) have also been reported.

The main physical findings in peritoneal mesothelioma are, increased abdominal girth and abdominal mass. The patients are usually febrile and look chronically ill and pale.

Following aspiration of abdominal fluid, accumulation will recur shortly afterwards. In the later stages, complications such as intestinal obstruction, obstructive hydronephrosis and bilateral lower limb oedema may develop (5, 78). Abdominal hernia or hydroceles are found in most of them.

RADIOLOGY

The chest radiography almost always reveals pleural effusion (109). The radiological findings in pleural mesotheliomas may be summarized as follows:

1. Pleural effusion: Massive, occupying half or more of the hemithorax and obscuring the pleural tumor, or localized. Mediastinum fixed or pushed to the opposite side.
2. Lobulated pleural thickening which may reach up to the apex.
3. Frozen chest: Intercostal space narrowing, shoulder droping, scoliosis.
4. Satellite lesions along with pleural abnormalities, i.e., fibrosis, pleural plaques, pleural thickening on the same side or other side.
5. In the late stages of the disease, the chest x-ray may show mediastinal widening, enlargement of the cardiac shadow due to infiltration of the pericardium and destruction of ribs or soft tissue masses.
6. Pneumothorax, hydro-pneumothorax: In these conditions, lobulated masses can be easily seen on the costal pleura.

Computed Tomography (CT) is ideal for the detection of pleural abnormalities (60, 63, 95) and has great sensitivity for the diagnosis of pleural mesothelioma. Chest CT scans should be obtained in all patients in whom malignant mesothelioma is considered (2). The CT scan reveals that the pleura is thickened, with an irregular, often nodular internal margin that serves to separate this tumour from other types of pleural thickening. These changes are mostly seen at the base of the lung. Computed tomography usually shows marked thickening of the major fissure due to a combination of fibrosis, tumour, and fluid. The fissure may also appear nodular because of tumour infiltration. At times, pleural thickening is seen predominantly along the mediastinum. In such cases, the pulmonary margin is irregular and discrete nodules may be seen in the juxtamediastinal tissue. Small pleural effusions and subpleural tumour nodules are readily seen and CT scan can demonstrate asbestos pleural plaques and calcifications which are not visible on conventional films.

The CT directed biopsy or aspiration from loculated pleural collection can be used in some cases. Computed tomography cannot distinguish the composition of different fluid collections, nor are density coefficients specific enough to separate a homogenous pleural mass from a fluid loculation. The CT is of little benefit in initial detection of benign or malignant lesions of the chest wall. When chest wall metastases are suspected because of clinical findings or a positive bone scan, CT demonstrates a number of lesions even though plain films may be normal.

In the diagnosis of malignant peritoneal disease, plain abdominal films, barium meal and follow-through and barium enema show extrinsic pressure and stenotic lesions. Ultrasonography and CT scanning can give an idea of the extension of the tumour (30). Definite diagnosis of malignant peritoneal mesothelioma can be made at laparoscopy with either biopsy or cytology. Sometimes a tissue diagnosis can be made only at laparotomy.

The clinical picture of pericardial mesothelioma is related to cardiac or pericardial symptoms, heart failure, or arrhythmias. Some cases are localized at the atrioventricular node (45). The tumour may compress the pulmonary artery or coronary arteries causing coronary arterial symptoms. Radiological examination shows only an enlarged heart shadow.

Laboratory Findings: The pleural fluid is mostly pleomorphic, that is, it may be serous, sero-hemorrhagic or hemorrhagic depending on the stage of the disease. The fluid is exudative and may have reduced glucose and pH levels if the tumour is large. At times, the pleural fluid of patients with malignant mesothelioma is viscid, owing to the presence of large amounts of hyaluronic acid. Rasmussen and Faber (96), measured the levels of hyaluronic acid in the pleural fluid of 247 patients, 19 of whom were due to malignant mesothelioma. They found that pleural fluid hyaluronic acid levels above 0.8 mg/ml occurred only in patients with mesothelioma. Only 7 of their 19 patients with mesothelioma had high levels. For this reason, determination of hyaluronic acid in the pleural fluid is not very useful. Cytologic examination of pleural fluid shows normal mesothelial cells, differentiated and undifferentiated malignant mesothelial cells and a number of lymphocytes and polymorphonuclear cells. Although the pleural fluid cytologic test can suggest the diagnosis, it must always be confirmed by tissue diagnosis.

The sedimentation rate may be normal or high (37, 64) and there may be a slight anemia. In some cases, *hypergammaglobulinemia* (87), *eosinophilia* (33) and *thrombocytosis* (43) may occur in peritoneal mesotheliomas. The *syndrome of inappropriate ADH secretions* has been described (88) and it has been suggested that this may be due to mechanical stimulation of vagal nerve with reflex secretion of ADH. One of the rare features is *hypoglycemia* which manifests itself with neurological features, such as a tendency to sleep, excessive sweating, tremor, muscular twitching, hypothermia and manic reactions (11, 88).

DIAGNOSIS

A comprehensive and detailed history is essential for the diagnosis of mesothelioma. It should be considered in a middle-aged or older patient with persistent chest pain and dyspnea especially if there is a history of asbestos exposure. This diagnosis should also be considered in cases of chronic exudative pleural effusion.

If clinical and radiological findings suggest mesothelioma, a CT scan should be done. Law and co-workers (63), reported that there is good correlation between positive CT scan and thoracotomy and autopsy findings. The CT scan was however not superior to plain chest radiographs in the delineation of the tumour. The greater sensitivity of CT was of limited value when the tumour was extensive, and furthermore it was not suitable for the detection of diaphragmatic involvement. In localized pleural effusion, CT guided biopsy is especially necessary for positive results.

Pleural fluid cytology is of limited diagnostic value and is only useful in raising a suspicion of mesothelioma and adenocarcinoma certain special studies should be done on the pleural fluid namely, PAS staining, CEA, keratin and hyaluronic acid measurements (6, 27, 52, 125, 126, 127). Table 9 shows the results of these studies.

Table 9: Studies of pleural fluid and/or cells useful in differential diagnosis of adenocarcinoma and mesothelioma (97)

Study	Adenocarcinoma	Mesothelioma
PAS (cells only)	Strongly positive	Negative
Cancinoembryonic antigen (Cells and fluid)	Strongly positive or 30 ng/ml	Weakly positive or 5 ng/ml
Keratin (cells only)	Negative or weak peripheral staining pattern	Strongly positive with homogenous staining pattern
Hyaluronic acid (cells and fluid)	Negative	Positive

If one is dealing with a case in which cytologic and biopsy studies are negative or inconclusive, but there is still a strong possibility of malignancy, one may need to do chromosomal studies on the pleural fluid (44, 70).

Pleural biopsy is indicated whenever analysis of a pleural exudate yields non-diagnostic findings. Abram's needle is safe and obtains slightly larger tissue specimens than other needles. Many specimens can be taken from one puncture site with the needle directed in a semicircle facing the lower rib. Some of the samples should be examined histologically and others cultured for acid-fast bacilli and fungi.

The diagnosis of malignancy can be confirmed by the findings of closed pleural needle biopsy in 40-70% of cases (80, 99). This increases to 90 percent when biopsy results are combined with cytologic findings (99).

Thoracoscopy is the most useful diagnostic method in cases of exudative pleural effusion where cytology and needle biopsy have been unhelpful. During thoracoscopy, the operator should closely examine the pleural cavity, the apex, diaphragm and pericardium, for tumour nodules, masses, pleural thickening, hyalinized or calcified pleural plaques and must take multiple biopsies from any suspicious areas. The most common thoracoscopic findings in malignant mesotheliomas are, diffuse shiny grape-like appearances, solitary nodules, and pleural irregularities due to formation of hyalinized or calcified plaques (7, 19).

Thoracoscopy is also useful for the early diagnosis and staging of malignant mesotheliomas. It is less invasive than thoracotomy and complications are relatively rare. The observed complications are, re-expansion of pulmonary edema during the aspiration of air and fluid from the pleural cavity, bleeding, empyema and recurrence of the tumour at the thoracoscopy site (7, 19).

If the stage of disease is beyond surgical treatment and fluid accumulation is rapid, sclerosing procedures can be carried out during thoracoscopy (7).

Thoracotomy should be the last method for the diagnosis of pleural mesothelioma. It should be reserved for patients who may be suitable for surgical intervention.

Malignant mesothelioma often infiltrates needle tracts, thoracoscopy and thoracotomy scars and chest-tube drainage sites. One should therefore avoid repeating such procedures in patients with suspected mesotheliomas who are suitable for surgery (37).

DIFFERENTIAL DIAGNOSIS

Non-malignant causes of pleural effusion such as infections, pulmonary embolism, connective tissue disorders and other rare causes pleural disease should first be excluded. Furthermore, other important conditions such as benign asbestos pleural effusion and thickening, benign mesothelioma, primary bronchial tumours, secondary adenocarcinoma arising from the gastrointestinal tract, carcinoma of the breast and ovarian carcinoma should also be excluded.

PROGNOSIS

The prognosis of malignant mesothelioma is poor. Although there are a few cases who have lived for more than 7 years, in general, the median survival time in the majority of reported cases ranges from 4 to 12 months and from 8 to 14 months after the onset of symptoms (4). Survival is also related to the stage of the disease. Butchard and colleagues (21),have proposed a system for staging mesothelioma.

From table 10, it is clear that for purposes of staging extensive investigations are needed. These include a barium swallow to assess esophageal involvement; a bronchoscopic examination to assess involvement of tracheobronchial system; CT scan of the chest to assess mediastinal and chest wall involvement; brain, liver and bone scans to search for blood-born metastases and finally, a pneumoperitoneogram to delineate diaphragmatic penetration.

Table 10: Pathologic Staging of Diffuse Malignant Mesothelioma of the Pleura (21)

Stage	Manifestation
I.	Tumour confined within the capsule of the parietal pleura, i.e., involving only the ipsilateral pleura, lung, pericardium, and the diaphragm.
II.	Tumour involving chest wall or mediastinal structures; possible lymph node involvement inside the chest.
III.	Tumour penetrating the diaphragm to involve the peritoneum; contralateral pleural involvement; lymph node involvement outside the chest.
IV.	Distant blood-born metastases.

At the time of diagnosis, the median survival times for stages I, II, and III disease are 10 months, 9 months, and 5 months, respectively (4).

Epithelial mesothelioma has a better prognosis than the others (121). On the other hand, the report of McCormic and co-workers (72), suggest that the mesenchymal variant has the best prognosis. However, Levis et al. (68), believe that if enough samples are examined all mesotheliomas will be classified as the mixed variety.

MANAGEMENT

Surgery: The management of patients with malignant mesothelioma is very difficult. Surgical management appears to be the only hope for possible cure for the patients. However, the optimal surgical approach and the type of surgery for malignant mesothelioma is controversial. Lewis and associates (68), reviewed their experience with mesothelioma and concluded that attempts at partial or complete resection are not indicated. This conclusion was also shared by Gaensler and his colleagues (46). Wanebo and co-workers (121), performed pleurectomies on 33 patients of whom 17 had the epithelial and 16 the sarcomatous variant. Four of the 17 patients with epithelial variety and three of the 16 with the sarcomatous type were disease free at 17 to 69 months post-operatively. These authors followed their surgical procedures with radiotherapy or chemotherapy because tumour was left behind when pneumonectomies were not performed. Others suggest that an extrapleural pneumonectomy should be performed because the mesothelioma in most cases invades the visceral pleura and the underlying lung. Butchart and associates (21) from the U.K., recommend a radical extrapleural pneumonectomy in which the ipsilateral pericardium and diaphragm are also removed. They operated on 29 patients and reported that 2 patients were alive without evidence of recurrence 3.5 and 6 years after operation. Their post-operative mortality rate was however 31%. They concluded that radical pleuropneumonectomy is only indicated in those patients under the age of 60 who are fit and who have stage I epithelial type tumour.

Good results have been claimed by palliative decortication in cases where an exudate rapidly recurs necessitating repeated thoracocentesis (71, 94).

Chemotherapy: The role of chemotherapy in the treatment of mesothelioma remains to be defined. Unfortunately, not enough patients have been studied to evaluate the long-term survival rate. Trials have also not taken into consideration the histologic form or stage of the disease. Furthermore, until recently, there were no objective methods, such as CT of chest, for follow-up of patients.

Doxorubicin (Adriamycin) appears to be the most active single agent against malignant mesothelioma. In a series of 36 patients reported by Aisner and Wiernick (1), 16 patients had some regression and 4 patients had stabilization after the administration of doxorubicin. As single agents, alkylating drugs such as cyclophosphamide, mechlorethamine, melphalan and 5-fluorouracil or procarbazine all seem to be effective in some cases.

Combination chemotherapy has also been tried for malignant mesothelioma, but so far there is no strong evidence to suggest that a combined regimen is more effective than therapy with doxorubicin alone (1).

It has been claimed that good responses, as measured by tumour regression and alleviation of symptoms occur in up to 50 percent of treated patients (3, 24).

Radiotherapy: As with chemotherapy, past results with radiotherapy are difficult to interpret on account of the lack of objective parameters.

The use of high dose external radiotherapy in malignant mesothelioma has been reported and the results seem promising (42). The median survival was 11 months. A good palliative effect with shrinkage of tumour or reduction of pleural fluid and sometimes pain relief were achieved. Metastasis can also be treated with radiotherapy if it is painful.

The rightful place of radiotherapy in the management of malignant mesothelioma remains to be determined. According to the work of McCormack and associates (72), intersititial radiotherapy appears to be beneficial, at least in patients with the epithelial type of mesothelioma. A combination of this approach with surgery, external radiotherapy and chemotherapy resulted in a disease free period of 4 to 53 months after diagnosis in 7 (21%) of their 33 patients.

Malignant mesotheliomas are generally accepted as "radio-resistant" tumours. Fast neutron therapy is suggested for hypoxic radioresistant cells and high rates of complete regression have been achieved in a variety of tumours, such as, soft tissue sarcomas. Blake, Catterall and Emerson (16), reported a case of pleural mesothelioma Stage II, given Fast Neutron therapy and he was free of recurrence for 78 months.

Controlled trials, which among other factors, take into consideration careful histologic classification and staging of malignant mesothelioma are needed to define the correct place of radiotherapy in the management of mesothelioma.

Palliative treatment: Dyspnea and chest pain are the most difficult to deal with. Substantial relief of shortness of breath in patients with large pleural effusions can be achieved with therapeutic thoracentesis. Removal of 1 to 2 liters of fluid at weekly intervals is effective in relieving the dyspnea. Initial aspiration of more than 750 ml. may cause discomfort and aspiration may become progressively more difficult as tumour progresses to occupy the entire pleural space (37). Recurrent pleural effusion normally terminate with decortication, but a less invasive technique may be preferred, particularly in advanced cases. Intrapleural tetracycline, bleomycin or other sclerosing agents, preceeded by aspiration to dryness and followed by suction has been found effective in some cases (64, 97, 120). If a malignant effusion's pH is acidic and its glucose content is low, the pleura is likely to be infiltrated by tumour. In such cases sclerosing procedures are usually ineffective. The thick tumour peels and prevents the inflammatory reaction needed to seal the visceral and parietal pleura. Chest tube drainage often creates pneumothorax, because the lung, incarcerated by tumour, is unable to expand to meet the pleura. In such patients palliative pleurectomy may be used.

Pleural effusion due to malignant mesothelioma that is not causing dyspnea or circulatory impairment requires no special local therapy. Clinical observation is the best course of action in patients with such effusions.

Severe chest pain in mesothelioma is mostly due to tumour invasion of the chest wall. In such patient, local palliative radiotherapy may relieve the pain. Neurosurgical procedures for pain control have been found ineffective (64, 104). If the pain cannot be well controlled with non-narcotic analgesics, regular opiates must be given.

In conclusion, the management of malignant pleural mesothelioma is difficult and requires a lot of care. If the tumour is confined to one hemithorax, extrapleural pneumonectomy is recommended. If the tumour cannot be completely removed, interstitial radiation should be given in combination with external radiotherapy. If measurable residual disease is present, a trial of doxorubicin is warranted.

Cooperative international studies in which the tumours are carefully staged and classified histologically are needed in order to determine the optimal treatment for malignant mesothelioma.

MANAGEMENT OF MALIGNANT PERITONEAL MESOTHELIOMA

Malignant peritoneal mesothelioma has a progressive and virulent course and is uniformly fatal (78). Recently, Antman and colleagues (5), intensively treated 14 cases of peritoneal mesothelioma and obtained significantly better survival results especially in patients under 40 years of age. Their regimen included surgical debulking with intraperitoneal doxorubicin together with combined chemotherapy and whole abdominal radiotherapy or I.V. doxorubicin and cyclophosphamide and/or intraperitoneal doxorubicin and cis-platinum. Nearly half of the patients treated intensively, remain alive with no CT scan evidence of disease at 9-36 months.

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BENIGN MESOTHELIOMAS

Benign mesotheliomas are uncommon tumours of pleural and peritoneal cavities. Up to 1975, 170 cases of benign pleural mesothelioma had been reported (5). Recently, over a 25 year period, 52 cases were seen at the Mayo Clinic (6).

Most patients with benign pleural mesothelioma have no history of asbestos dust exposure (2, 6) and at present there is no evidence of any association between the two.

Pathology: These tumours are firm, encapsulated and yellow in colour (4). About 70 percent of them arise from the visceral pleura and they eventually invade the lung and chest wall locally (3). Histologically, there are 3 types, namely fibrous, epithelial and mixous.

Clinical Features: Nearly half of the patients are asymptomatic, and so the tumour is usually detected on routine chest radiograph (2, 6). Some patients may, however, complain of cough, chest pain and a rolling sensation in the chest and about 25 percent of them may have fever without infection.

Paraneoplastic syndromes such as hypertrophic pulmonary osteoarthropathy are seen in approximately 20% of patients but with large tumours the incidence is much higher. Okike, Bernatz and Woolner (6), demonstrated that 10 out of 11 patients with tumours greater than 7 cm. in diameter had hyperthrophic osteoarthropathy, whereas none of the 41 patients with smaller lesions had the syndrome. When the tumour is surgically excised, the symptoms of paraneoplastic syndrome are immediately relieved (6).

Another syndrome which is seen occasionally in benign fibrous mesothelioma is hypoglycemia. In a review of 360 cases of benign fibrous mesothelioma, symptomatic hypoglycemia was reported in 4 percent (2). The mechanism of the hypoglycemia is not clear but most probably the utilization of glucose by the tumour and the inhibition of lipolysis and hepatic gluconeogenesis by products of the tumour may account for this syndrome. Occasional syncopal attacks, coma, aphasia, hemiparesis and manic reactions have been observed in some patients with hypolycemia (5). Surgical removal of the tumour also relieves the hypoglycemia.

Radiology: These tumours appear as solitary, sharply defined, discrete, occasionally calcified masses, located at the periphery of the lung or related to the fissures (1, 4). They are frequently lobulated and may be associated with pleural effusion. The tumour may sometimes be very large enough to occupy the entire hemithorax and shift the mediastinum.

Diagnosis: Most of the benign mesotheliomas are diagnosed only by thoracotomy.

Treatment: The treatment for benign mesothelioma is surgical. If the tumour originates from the visceral pleura, substantial amounts of lung parenchyma may have to be removed with it (6). Surgical resection cures nearly 90 percent of patients, but recurrent disease occurs in the remaining 10 percent (2, 6) and so it is recommended that annual chest x-ray screening should be done postoperatively.

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BRONCHIAL CARCINOMA

Carcinomas in man arising from occupational, environmental or indirect exposure to asbestos are called "Asbestos Related Carcinomas".

History: During the period when asbestos was carelessly used and no preventive measures were taken, most workers lost their lives through asbestosis which was complicated by infection and respiratory failure. When preventive measures were introduced, workers began to live longer. It was work dating from this period that drew attention to the high incidence of bronchial carcinoma in asbestosis. Wood and Gloyne (24), collected 12 cases of bronchial carcinoma among 100 cases of asbestosis. In the research carried out by Nordmann and Sorge (17), on the autopsies of asbestos workers, they collected bronchial carcinoma in 12-20% of cases. Amongst those with cancer there were a number under 35 years of age. Tumours were seen in the lower lobes of the lung and in the periphery. Lung cancer at routine autopsy was 0.8-2.4%, therefore the high figures obtained in autopsies on asbestos workers reflected the relationship between asbestos and primary lung carcinoma.

Epidemiological and Mortality Studies: The studies of Doll (4), Knox et al. (10) and Peto et al. (18) and others (12, 13) had demonstrated that there was a 2-3 fold excess of lung cancer in those workers first employed between 1933 and 1950 and in those first exposed in 1951 or later.

A seven-fold excess of lung cancer was found in a group of insulation workers exposed to chrysotile and amosite but not to crocidolite (19, 20). Enterline et al. (5), reported 4.3 times increased risk of respiratory cancer mortality among maintenance workers and 1.7 times increased risk among production workers exposed to mixed asbestos who had reached retirement age.

Newhouse (14-16), showed that the cancer risk following mixed exposure of workers to chrysotile, amosite and crocidolite is dose related. Those workers reported to have had heavier exposures showed excess of lung cancer (6 times for men, 12 times for women) after 15 years, whereas those with moderate or low exposures required 25 years to demonstrate an excess.

McDonald et al. (73, 74), also showed an increased risk of lung cancer in Canadan chrysotile asbestos workers.

Kogan et al. (11), studied the cancer mortality among workers in asbestos mining and milling industries between 1948 and 1967. The total cancer mortality rate among the workers was 1.67 times higher than that of the general population.

Selikoff et al. (20), calculated that asbestos workers who smoke had 8 times the lung cancer risk of all other smokers and 92 times the risk of non-smokers who did not work with asbestos. This study had been interpreted as being consistent with the synergistic effect of the carcinogens, smoking and asbestos. Some studies are consistent with the occurence of an increased risk among non-smokers but with a lower order of magnitude.

According to some epidemiological studies (14, 16), the dose response relationship is linear, but is steeper for those in asbestos manufacture than for those in mining. The increased risk appear at about 2 to 30 years, although obviously there is an interaction between age and lung cancer mortality.

Gaensler and associates (7) followed up, 1, 577 persons with asbestos exposure from 3 to 30 years and detected that 23 developed bronchogenic carcinoma.

Multiple primary cancers have been published in asbestos workers. Dohler et al. (3), reported on 5 shipyard workers exposed to asbestos. Two had both lung carcinoma and colon carcinoma and 3 had 2 distinct pulmonary carcinoma each.

Pathogenesis: There is no concensus of opinion regarding the mechanism of asbestos-induced cancer. Cancers have been said to develop secondarily to the pulmonary fibrosis caused by asbestos (1, 6, 19, 22).

The synergistic effects of Benzo-a-Pyrene (BP) with asbestos have been explained by absorption of BP to the fibre, leading to greater retention of the material in the lung. Asbestos given intratracheally in animals resulted in more cancer if BP was added (21).

Trace metals, which occur naturally with asbestos or can be added to it during milling, have been suggested to be the cause of bronchial carcinoma (2, 9).

Asbestos induces an increased permeability of cellular membranes which might lead to an increased inflow of carcinogenic materials and causes chromosomal alterations (8). These biological changes may lead to carcinogenesis.

Pathology: Asbestos-related cancers of the bronchus are generally localized to the lower lobes and peripheries of the lungs and they frequently involve the pleura. Although Gaensler et al. (7) believe that the histological structures of these types of cancer do not differ Whitwell, Newhouse and Bennet (23) inform us that adenocarcinoma arising from the distal airways are seen in high proportions of about 34 percent of asbestos workers.

Clinical Manifestations: The clinical symptoms and signs of asbestosis can generally mask the initial features of neoplasm. In such patients, dry cough, localized chest pain, hemopthysis, and weight loss all suggest the presence of neoplastic disease. On the other hand, the clinical manifestations of asbestos-related bronchial carcinomas are not different from non-exposed smoker patients with primary bronchial carcinoma.

Radiology: The tumours are mostly localized in the peripheral part of the lower lobes and usually associated with lung fibrosis. Chronic fibrosing pleuritis and pleural calcification in the chest x-rays of the patients are helpful in diagnosis.

Diagnosis: Diagnostic methods applicable in other lung cancers are also relevant here. In endoscopic examination, the peripheral localization of the tumour decreases the chances of obtaining a positive result. Since it may lead to tumour implantation in the chest wall, percutaneous lung needle biopsy is not advised.

Occupational history and environmental information along with clinical and radiological findings are important in the diagnosis of asbestos-induced lung cancers.

Prevention: The recommendations for asbestosis are applicable here as well. However, it should be emphasized that asbestos workers must, on no account, smoke.

Treatment: Surgical resection of tumours in asbestos-related cancers are rather limited. Obvious or latent fibrosis is responsible for this limitation.

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GASTROINTESTINAL CARCINOMA

The etiology of gastrointestinal cancers is not clear but epidemiological studies have implicated some external agents. Included in the list of suggested carcinogenic agents are a high cholesterol diet, meats, salted fish, pickled vegetables and alcoholic beverages. Most authors now agree that a combination of different agents and mechanisms are more likely to be responsible than any single agent.

Many studies have shown that more than the expected proportion of digestive tract cancers occur in asbestos workers. Gloyne (4), reported on 102 autopsy cases of asbestosis and found eight cases with gastrointestinal cancers, even though the average age of the patients was only 35.5 years. Selikoff, et al, (14, 15) reported on 632 asbestos insulation workers who had been followed from 1943 to 1962, 29 of them developed digestive tract cancer, the expected number was 9.4. On further follow up in 1973 there were 41 deaths from gastrointestinal cancer as compared to an expected number of 13. The time interval from first exposure to asbestos to diagnosis of cancer was more than 20 years. Gastric cancer especially was six times more than expected, but cancer of the colon was 3 times more. Newhouse (12), found a significant increase in gastrointestinal cancers in males in a London textile factory. Elmes and Simpson (3), have also demonstrated an increase in the incidence of this type of neoplasm. With increasing exposure to asbestos an increasing number of cases of gastrointestinal cancer has been observed in Canada (9). Borow et al. (1), presented 12 cases of gastrointestinal cancer among 90 cases of asbestosis.

Miller (11) and Schneidermann (13), have reviewed published articles on this subject and they concluded that, there was no doubt about the increased risk of digestive system cancer among persons exposed to asbestos and that the induction period was usually more than 20 years.

It is accepted that hyalinized or calcified pleural plaques are the proof of asbestos exposure. Hillerdal (7), noted that, 80 percent of pleural plaque carriers will readily admit to asbestos exposure, and of the rest a large portion will probably have been exposed unknowingly. His study revealed a slight but significant excess of typical pleural plaques in patients with gastrointestinal carcinoma, particularly those of the esophagus and stomach (8).

Pathogenesis: Asbestos fibers can reach the gastrointestinal tract by swallowing. Some of the inhaled asbestos dust particles that are deposited in the upper digestive tract quickly reach the stomach (5). Cunningham and associates (2),have shown that the number of fecal asbestos is significantly increased among asbestos workers. Most of the ingested fibers pass through the gastrointestinal tract, but some probably penetrate the intestinal cells. However, Gross et al., believe that asbestos fibers do not penetrate into digestive tract cells (5). There are thus conflicting results in experimental studies on ingestion of asbestos fibers.

Ingestion of asbestos in food, beverages or drink can occur. Asbestos fibers are also found as ingredients in many processed foods. Merliss (10),suggested that talc-coating of rice is the factor responsible for the high occurence of stomach cancer in Japan. But this view has not been supported by epidemiological studies (6).

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OTHER ORGAN CARCINOMAS

Epidemiological studies and case reports have shown excess risk of other organ cancers in asbestos workers. However, these cancers occur relatively rarely in relation to other asbestos cancers.

Laryngeal Cancer: Stell and McGill (13), reported that of 100 men with squamous-cell carcinomas of the larynx, 31 had known exposure to asbestos, compared to only three in matched controls. Similar observations have been reported by other authors (8, 12). Newhouse and Berry (10), found two cases of cancer of the larynx in their cohort of over 4000 workers, compared to an expected incidence of 0.4. Bianchi, et al. (1) and Hinds, et al. (6), have also shown a slight but not significantly increased exposure to asbestos among patients when compared to matched controls.

Hillerdal (7), studied retrospectively laryngeal carcinomas occuring over a 10 year period. In 14 of 156 available chest x-rays he detected typical asbestos related pleural plaques which was very significantly more than was expected in the region. He suggested that all patients with laryngeal carcinoma should be questioned about asbestos exposure, and that laryngeal carcinoma in patients who are occupationally exposed, should be considered an occupational disease.

Recently Newhouse (11), studied 83 male and 15 female patients with laryngeal carcinoma. In the females, only 2 had asbestos exposure and in the male group, only 6 gave such a history. Among the males, cigarette smoking was significantly more common. She compared these findings with those of other patients who had laryngeal diseases such as cysts, polyps and inflammatory disorders and those without laryngeal disease and concluded that asbestos exposure was not more common in the neoplastic group than in the three other groups.

Other Organ Cancers: There are a few case reports which point to the relation of asbestos to different malignancies such as sarcomatous tumours (2, 3), ovarian malignancies (4, 5), oropharyngeal tumours (5, 6) and breast carcinomas (3).

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ASBESTOSIS

Diffuse, progressive and irreversible interstitial lung fibrosis due to inhalation of asbestos dust is called "Asbestosis". Other synonymous terms are "Parenchymal Asbestosis" and "Asbestos Related Pneumoconiosis".

Early reports of pulmonary fibrosis caused by asbestos inhalation were by Murray in 1907 in the U.K., Hoffman in 1918 in Canada, and Pancoast, et al. in 1917 in the U.S.A. However, the first complete descriptions of asbestosis were reported by Cooke in 1924, McDonald in 1927 in the U.K., and by Mills in 1930 in the U.S.A. (12, 14). Later on Wood and Gloyne (31) collected 100 cases in 1934, and Stone (24) 180 cases in 1940.

Asbestos related lung fibrosis was also detected in rats, monkeys, and dogs living near asbestos mines and in donkeys carrying asbestos ore (21, 29).

Pathology: The disease starts in the small airways and then spreads to a form of diffuse fibrosis. The respiratory bronchiole is the main obstacle through which asbestos fibres have to pass, and fine fibres will tend to deposit there. These processes have been demonstrated in animal experiments (28). Changes in the alveolar membranes are usually minimal, however, there are important capillary involvements which lead to diffusion defect.

Lung fibrosis due to asbestosis occurs mostly in the lower lobes. It has been claimed that the asbestos fibres cannot turn the corners and therefore localise in the lower lobes. This is opposite to the localisation of non-fibrous minerals such as silica.

In the later stages, along with fibrosis, bronchiolectasis, pleural thickening and plaque formation and carcinomas are found.

Early studies led many investigators to conclude that those exposed to asbestos dust developed asbestosis, if the dust concentration is high or if the exposure time is long. It is now believed that slight exposure can lead to minimal fibrosis. There is no correlation between the asbestos fibres and the degree of fibrosis (17). Once the pathologic changes have reached a certain level, it will progress even if no further exposure takes place. Asbestosis can even appear many years after the patient has left the asbestos related occupation.

Clinical Manifestations: The most commonly encountered symptom is shortness of breath on exertion. Most authors believe that asbestosis is a monosymptomatic disease. In some patients, particularly those who are smokers, productive cough, mainly in the morning may be observed. However, in an asbestos worker who does not smoke, cough productive of sputum always suggests either infection or tumour. In some patients there is permanent chest pain localized in the lower parts. This symptom may be related to chronic cough or other asbestos related chest diseases. Loss of appetite and cachexia have also been reported in some cases.

Positive findings on chest examination are, tachypnea, decreased expansion of chest and fine crepitations. The other synonymous terms for fine crepitations are, "Velcro rales", "End-Inspiratory Crackles or Rales" and "Cellophan" rales. They are high-pitched explosive sounds that are usually heard in most diffuse interstitial lung diseases, e.g. fibrosing alveolitis, and interstitial pulmonary edema. They are also heard in poorly ventilated territories of the lung, or in healthy subjects during the first few inspiration after prolonged shallow breathing. Their distribution is mainly basal and symmetrical, within a band surrounding the chest from the costal margin to the horizontal upper boundary. They often start late and become more profuse towards the end of inspiration. One of their most striking features is a recurrent pattern in consecutive respiratory cycles, identified by the relative loudness and spacing of individual crackles. They are poorly transmitted, so their pattern changes when the stethoscope is moved over a short distance. They are seldom audible at the mouth. When the patient bends forward, Velcro rales often stop immediately and then return but are more sparse. They, however, do not disappear completely.

Finger clubbing is found in only one third of the patients (14). In the later stages, cyanosis as a result of ventilation perfusion imbalance develops. If pulmonary hypertension has developed, the second heart sound in the pulmonic area will be loud and there will be signs of right ventricular failure such as elevated JVP, hepatomegally, ascitis and peripheral oedema.

Graeves (8), reported a case of Caplan's Syndrome in an asbestos worker.

Pulmonary Function Tests: Abnormalities of lung function can occur before any radiologic changes. Restrictive pulmonary function pattern as seen in most diffuse interstitial lung disease is also typical of asbestosis. There will, be reduced diffusion capacity due to ventilation-perfusion mismatch.

Since asbestosis starts in the small airways, early obstructive changes are also expected in this disease. Becklake et al. (1), demonstrated an increase in residual volume in association with early parenchymal radiologic changes, but a decrease in more advanced stages, which might indicate an early obstructive change that is later obscured by increasing restrictiveness.

The tests for measuring small airways changes may be used in early screening of asbestos workers, provided that they are non-smokers. Smoking can cause small airways obstruction and fibrosis. A combined effect of smoking and asbestos has been demonstrated (1). Rossiter and Berry (20), mentioned that crepitations and radiologic fibrosis in workers with more than 20 years of exposure to asbestos were unknown or very rare in non-smokers but occured in 19 percent of heavy smokers.

Radiological Changes: The radiological findings and a combined pathological-radiological correlation have been described by Caplan et al. (2).

In the early stages of asbestosis some clinical and functional changes can be detected without any radiological abnormalities. As a rule primary radiological findings are thin reticular motling in the lower parts of lung. If pleural changes are present in addition to reticulation, a diffuse haze of the lower parts of the lungs "Ground Glass Appearance" is noticed. With fibrosis of the peripheral parts of the lungs, the diaphragmatic domes are obscured and there is a "Shaggy" heart appearance (2, 7, 13, 25).

In some cases, other asbestos related diseases such as pleural plaques, pleural thickening, pleural effusion or carcinoma may also be detected (2, 7, 13, 25).

Atypical asbestosis such as apical localizations, nodular changes and massive upper lobe fibrosis (9, 19) have also been reported.

Laboratory findings: Increased frequency and levels of Antinuclear Antibody and Rheumatoid Factor have been reported in patients with asbestosis (23, 26). It was suggested that nonspecific stimulation of the immune system and activation of macrophages could initiate lung fibrosis.

Bronchoalveolar lavage (BAL) done in asbestos workers showed increased activity of lysosomal enzymes believed to have been released from activated pulmonary alveolar macrophages (15, 30).

Another immunologic abnormality reported in asbestos workers is depressed function of T lymphpcytes (16).

Diagnosis: The first and most important step in the diagnosis of an asbestos-related disease is a carefully taken and comprehensive occupational or enviromental history.

The clinical findings, functional abnormalities and radiological changes may suggest asbestosis.

Inhaled asbestos fibres in the lungs may be bare or coated. Only a very small proportion of the total number of asbestos fibres will be coated, and most of them are submicroscopic. The coated forms are called "Asbestos Bodies". These bodies have a central core with an iron-mucoprotein coat probably derived from macrophages. Under light microscopy they are rod-shaped and segmented with clubbed ends. The bare or uncoated fibers can only be seen by electron microscopy. At electron microscopy, up to 1000 times as many uncoated as coated fibres are seen. There is usually a crude correlation between the number of fibres and the number of asbestos bodies.

Only long fibres will lead to asbestos bodies. The asbestos bodies are not specific for asbestosis and their presence is diagnostic of asbestos-related disease only when there are other consistent findings such as interstitial fibrosis and pleural plaques. This is largely because necropsy studies have shown the presence of these bodies in the lungs of asymptomatic city dwellers (3-6).

Practically all asbestos bodies found in human lungs will contain amphiboles. Churg and Warnock (3, 5),found 86% of asbestos bodies in males to consist of amosite or crocidolite probably from occupational exposure, while 57% in females comprise of anthophyllite or tremolite, possibly from cosmetics.

Occupationally exposed persons show a higher frequency of asbestos bodies (3, 4). An increase in the incidence of asbestos bodies with time has been reported (27). There is also some correlation between the occurence of asbestos bodies and asbestos-related disease. Furthermore, the more asbestos bodies there are in the lungs, the greater the possibility of their presence in the sputum (10).

Histologic examination of biopsy material taken from the lung, through trans-bronchoscopic or transcutaneous lung biopsies or with thoracotomy is not enough for the diagnosis of asbestosis. Mineralogical studies using electron microscopy should be done as well on the specimens. By this method, the number of fibers per gram of dried lung tissue and their sizes will be recorded. All the fibers found in the lung tissue are not necessarily asbestos. Their structural analysis should be done with the Analytical Transmission Electron Microscope (ATEM).

Asbestos bodies have asbestos fibres in the core.There are several kinds of fibers which can be covered by protein material derived from macrophages. For this reason they are called "Ferruginous Bodies", since their core is not specified. Different studies have shown that, fibrous aluminum silicate, silicone carbide whiskers, carbon, sheet silicates and diatomaceous cosmetic talc and glass fibres can all produce ferruginous bodies (5, 6, 11, 18). Sebastien et al. (22),were the first to demonstrate, ferruginous bodies around zeolite (erionite) fibres in human lung samples.

There is no report of formation of ferruginous bodies around fine and short fibers such as attapulgite, mullite or rutile. This tends to suggest that only large and long fibres can produce these bodies.

Differential Diagnosis: There are several etiological types of diffuse interstitial lung diseases which share the same clinical, radiological, physiological and even histological appearances. They can be classified as, occupational and environmental lung diseases (Silicosis, extrinsic allergic alveolitis), drugs, radiation, infection related disease, interstitial pneumonitides and cryptogenic fibrosing alveolites, interstitial lung diseases associated with collagen diseases (Rheumatoid arthritis, Systemic sclerosis, etc.), alveolar hemorrhagic syndromes (Idiopathic pulmonary hemosiderosis, etc.) and others such as sarcoidosis, histiocytosis-x, etc.

In most patients a diagnosis of asbestosis can be made without biopsy but from the history of exposure, physical and radiologic findings. In patients whose clinical conditions permit, a lung biopsy may be done to confirm the diagnosis, especially if parenchymal findings alone are present without pleural plaques or if an alternative diagnosis is being considered, or if there are medicolegal implications.

The findings of asbestos bodies on cytologic study of sputum or transbronchoscopic lung biopsy indicates substantial exposure and may obviate the need for thoracotomy in some cases. Roentgenographic studies and pulmonary function tests are more sensitive than history and physical findings in detecting asbestos-related diseases. Computed tomography (CT) has a limited application in the diagnosis of asbestosis.

Management: Various international organizations have recommended that the permisible concentration of fibres, 5 microns or more in length, in the air at work places should not exceed 2 such fibres per millilitre of air. Further reduction to 0.1 fibre/ml. has been recommended.

Asbestos workers should be examined periodically and examination should include history to detect symptoms, chest x-rays and spirometry. There is no medical treatment of asbestosis. However, symptomatic treatment may benefit patients.

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IMMUNOLOGIC CHANGES

It is well known that the majority of asbestos workers who develop pulmonary fibrosis have been heavily exposed to asbestos dust for long periods, but it is equally recognized that there are a large number of people who have inhaled similar amounts of asbestos for comparable periods but who still remain healthy.

This divergence may be due to differences in immunological responses to asbestos fibre or to other as yet unknown mechanisms.

The immunological aspects of asbestosis is interesting. Increased frequency and levels of Antinuclear Antibody and Rheumatoid Factor have been reported in asbestos workers with or without asbestosis (12, 13). Greaves (3), reported the occurence of Caplan's syndrome in an asbestos worker.

Recent studies have shown that some asbestos-exposed workers, apart from increased levels of ANA and R.F., have lymphocytotoxic antibodies, non-organ specific antibodies, increased immunoglobulins and white blood cell changes.

Turner Warwick, et al. (14), studied certain immunologic parameters in asbestos workers and they concluded that: 1) The frequency of ANA and R.F., are increased in asbestosis. 2) Lung reactive autoantibodies are only slightly increased in those with heavy exposure but without lung disease. 3) In all the subjects referred to the Pneumoconiosis Medical Panel, London, for pension assesment, there is an almost linear relation between percentage of positive ANA and duration from the time of first exposure, with a plateau at 25-30 years. 4) There is an early stimulus to ANA production in some asbestos workers. 5) Lymphocyte sensitization to nuclear antigens is not found in asbestosis. 6) No evidence of lung-specific antibodies has been obtained. 7) Challenge of lymphocytes by asbestos fibre results mainly in cytotoxicity. She and her co-workers suggest that ANA acts as an accelerator once the fibrosis has been initiated by a separate agent.

Wagner et al. (15), tried to monitor immunologically an asbestos-exposed population in the U.K. Most of the tests concerned lymphocytes, their numbers and function. There were no significant findings in asbestos related carcinomas, but they detected decreased response in asbestosis, particularly in non-smokers. The opposite effect was observed in smokers, especially if they had recently smoked. They suggested that the changes were indicative of activity not severity, and that the effect of cigarette smoking may mask this effect.

Matej and colleagues (10),have studied HLA system and the consequences of long term asbestos exposure. Their results failed to give any statistical confirmation of an association between HLA-A, B antigens including B27 and asbestosis. However, they demonstrated a positive association of the disease and DR2 antigen in 24 workers with asbestosis.

Lange (7), studied autoimmunity and anergy in asbestos workers and concluded that besides increased frequency of autoantibodies, cellular immunity is also affected in asbestos related diseases.

Kagan and colleagues (4, 5), studied humoral and cellular immunity in asbestos workers and also found depressed cellular immunity in asbestosis. They however, demonstrated increased levels of secretory IgA, serum IgA and IgG in them. These parameters were low in those asbestos workers with pleural diseases but the number and percentage of T lymphocytes were decreased in those with asbestosis. Lymphocytotoxin which reacts in the cold was positive in 55 per cent of asbestos related pleural disease and 81 percent in asbestosis. They felt that, changes in T and B lymphocyte function and imbalance may initiate tumoural growth, especially when they detected 3 lymphoproliferative diseases (1 C.L.L., 2 multiple myeloma) among 26 asbestos workers who had been exposed heavily to asbestos dust (6). One of the patients with multiple myeloma later developed malignant pleural mesothelioma (11).

There are case reports that neoplasia of the haemopoietic system such as multiple myeloma, acute lymphoblastic and chronic lymphocytic leukemias have been found in asbestos workers (1, 2, 8, 9).

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PLEURAL EFFUSIONS

Pleural reaction such as thickening and effusion are frequently encountered in asbestos workers with lung fibrosis.

Wagner, Sleggs and Marchand (27), reported that some patients with malignant mesothelioma give a history of previous pleural disease. Between 1961 to 1965, Eisenstadt (5-7), reported on pleural effusion in asbestos workers and named it as "Pleural Asbestosis", or "Asbestos Pleurisy" or "Benign Asbestos Pleurisy". Collins (4), also published 2 similar cases who in addition had lung fibrosis. In the same year, McNulty (2), found 8 patients with bilateral pleural effusion in a small group of Australian asbestos workers. Two years later, Mattson and Ringvist (18), from Sweden diagnosed "monosymptomatic pleurisy" in 7 out of 42 male patients with calcified pleural plaques. In the same year, Webster (28), from South Africa demonstrated that 78.5 percent of asbestos workers had chronic nonspecific pleural thickening and he stated that some of these patients may have pleural effusion before the development of pleural plaques. He found pleural thickening only in 16.9 percent of gold mine workers. Gaensler and Kaplan (11), presented 12 cases of asbestos pleural effusion and concluded that, it should be considered as one of the so-called "Idiopathic Pleurisies". Later on there were case reports from Czechoslovakia, France and other countries.

In most patients with this type of pleural effusion there is a history of occupational or indirect exposure to asbestos. Exposure time varies from 10 months to 45 years (2, 11, 19). The time between last exposure and the development of effusion has been found in most cases to be 20 years but intervals of 2, 6 and 8 years have been observed (11, 13, 19).

A recent epidemiological study of asbestos exposed workers followed up for 3 to 40 years reported an incidence of 5.2 percent of otherwise unexplained effusions compared to none in an unexposed control group (10). In this study incidence was related to severity of exposure.

Clinical Presentation: Most of the patients are male and middle aged (2, 11, 13). Pleural effusion can occur suddenly or run a sub-acute or chronic course (3). The patients are often free of symptoms and the condition may be an incidental finding at chest x-ray screening (1, 3, 23). Some patients may complain of vague chest pain and breathlessness. The latter is due to pleural effusion associated with diffuse lung fibrosis. In addition to signs of pleural effusion physical examination may reveal digital clubbing and fine crepitations in cases with asbestosis.

Laboratory Investigations: Erythrocyte sedimentation rate is usually normal, except in cases with haemorrhagic effusion.

Pleural fluid may be small, but often amounts to as much as 2 litres. It is usually a sterile exudate and rarely haemorrhagic (1, 2, 11-13, 17, 18). In some cases eosinophilic effusion may occur. Cytologic study for neoplastic cells is usually negative.

Course: Asbestos pleural effusion usually persists for some months and may recur after aspiration. Recurrences may be either on the same side or on the opposite side. In some patients the effusion resolves spontaneously and is finally followed by diffuse pleural thickening or obliteration of the costo-diaphragmatic angles.

Radiology: Chest x-ray shows free or loculated pleural effusion with or without pleural thickening and/or pleural calcification. Other asbestos related diseases such as fibrosis may also be detected (11, 13, 15, 16, 21, 22, 25, 26).

Diagnosis: The diagnosis of asbestos pleural effusion depends on the history of asbestos exposure and the absence of any other etiology. Gaensler and co-workers (13), have based the diagnosis of asbestos pleural effusion on four criteria: 1) Direct or indirect exposure to asbestos; 2) An effusion confirmed by a transient pleural change in serial chest roentgenograms, by thoracentesis, or by thoracotomy; 3) Lack of evidence of any other disease associated with pleural effusion; 4) No malignant tumour detected within 3 years after the effusion.

Presumable diagnosis can be supported by the presence of lung fibrosis, pleural calcification and the detection of asbestos bodies in the pleura or lung tissues (11-13, 16-18).

Histologic examination of pleural tissues taken by either needle biopsy or thoracoscope shows chronic pleuritis with fibrosis. Analytical transmission electron microscopy is needed for the detection of asbestos fibres in the tissue.

Prognosis: Asbestos pleural effusions are benign. Pleural fluid usually disappears spontaneously or by simple aspiration (14, 19, 22-24). However in some cases, mesothelioma has occured after a long period (8, 9, 11, 13).

Differential Diagnosis: Malignant mesothelioma, metastatic pleural disease, tuberculosis, collagen tissue disorders, parapneumonic pleural effusions and drug induced pleural diseases must all be considered in the differential diagnosis. For histologic diagnosis, closed or open pleural biopsies, either with special needles or by thoracoscope are needed. During thoracoscopy or thoracotomy, in addition to pleural thickening, typical hyalinised or calcified plaques may be observed. Although these findings suggest benign asbestos pleurisy, they can also be seen in malignant pleural mesothelioma. In some cases, special investigations such as karyotype analysis of cells in the fluid, immunochemical staining and electron microscopy may be necessary.

Management: There is no concensus on the management of asbestos pleural effusion. Some authors are against surgical treatment, and advice follow-up, but on the other hand, Gaensler et al. (13), suggest thoracotomy and decortication for the following reasons; 1) For definite diagnosis; 2) To prevent re-accumulation of fluid; 3) To restore compromised lung functions; 4) To prevent malignant mesothelioma.

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PLEURAL PLAQUES

Cartilage-like plaques on the costal pleura due to asbestos exposure are called "Pleural Plaques". They are also known as "Hyalinized or Calcified Pleural Plaques", or "Pleural Hyalinosis".

History: The first description of pleural plaques was probably by Sparks in 1931 (6). Typical pleural plaques were, however, first described by Porro et al., in 1942 and Siegal et al. in 1943. Following these and especially after 1950, there were many publications on this condition in persons exposed to asbestos.

Etiology: The most common cause of pleural plaques is asbestos and it is now accepted that they are the objective sign of asbestos inhalation from occupational, or environmental exposure. They may appear from within 15 years to 30 years after first exposure. Generally, the longer and heavier the exposure, the more extensive is the development of pleural plaques, but in some cases even slight exposure may be sufficient to induce a reaction.

Pleural plaques may follow inhalation of any type of asbestos. Epidemiological studies in asbestos workers in different European countries, Canada and U.S.A. have demonstrated that nearly 5 percent of them have pleural plaques (2, 4, 5, 15, 16) but as high as 38% in insulation workers (11, 18).

Environmental asbestos exposure can also lead to formation of pleural plaques. This was first described by Kiviluoto in Finland in 1960 (10). Later, similar observations were made in Bulgaria, Czechoslovakia, and Turkey (1, 7, 14, 17, 19).

Apart from *asbestos; silica, talc, mica, calcimine* and *breunnerite* may also cause pleural calcification. The mechanism of the calcification in such cases may be related to contamination with asbestos (4).

Two types of minerals have been found to be responsible for the endemic plaques in Turkey, namely, asbestos and fibrous Zeolite (erionite) (7).

Pathogenesis: The pathogenesis of pleural plaques remains unknown and there are many hypotheses, which have been summarized by Hillerdal (6).

They include:

I. Mechanical:
   Small haemorrhages that later calcifiy.
   Asbestos needles scratching parietal pleura.
   Fibrin deposits that organize.
   Persistent slight hemorrhages from the visceral pleura.
   Excessive traction of the pleural from fibrotic lung.
   Transport of asbestos needles by gravity, stopped only by bone or tendon.

II. Lymphatic Transport of Needles:
   Blocking of hilar nodes by fibrosis, forcing lymph "backwards".
   Retrograde flow via mediastinal lymph nodes and parietal lymph vessels.

III. Blood Transport of Needles'
   Transport via blood, entrapment in the mesothelial tissue.

Pathology: Pleural Plaques are shiny white elevations with a sharp border. Microscopically, they consist of fibro-hyaline connective tissue, and are covered with normal mesothelial cell (8).

Clinical Features: Patients with plaques are usually asymptomatic. If, however, they have other asbestos related diseases such as pleural effusion, mesothelioma, asbestosis or bronchial carcinoma together with plaques, they may complain of chest pain and shortness of breath.

Radiology: Tangential Chest x-ray is the best method for the demonstration of pleural plaques. Oblique views are also useful for evaluation. In order to visualize non-calcified pleural plaques, a high kilovolt technique is preferable. Calcified plaques are generally much easier to recognize. They have a classical "Holy leaf" appearance in a frontal view. Diaphragmatic plaques, which progress slowly, are mostly linear and are localized on the medial part of diaphragm. In uncomplicated cases costadiaphragmatic angles are uneffected.

If pleural plaques are localized in the paravertebral area, conventional radiological techniques may not be helpful. CT scan will demonstrate these lesions very easily (9).

Pleural plaques are always more widespread and more numerous at autopsy than on x-ray (1, 8, 14). Only 10 to 15 percent are seen with conventional radiography (6, 8).

Differential Diagnosis: In the radiological differential diagnosis of pleural plaques, the following should be considered:

Fat Pads: Seen in obese persons. They start from the apices and continue to the costadiaphragmatic junction.

Intrathoracic Muscles: They are regular and bilateral.

Extrathoracic Muscles: They are regular, "Saw-shaped" and can be followed outside the thoracic cage.

Companion Shadow: They are soft tissue shadows along the ribs and are mostly seen at the apices.

Tuberculous Infection and Hemothorax: They are situated in the visceral pleura and at the periphery of diaphragm. They are usually unilateral.

Old Rib Fracture: There may be a history of trauma; relation with rib contour.

Silicosis: Mostly "egg shell" calcification of hilar lymph nodes. Very rarely pleural calcification.

Other Conditions: Calcification of secondary tumours (Multiple myeloma, malignant lymphoma, sarcoma, bone metastases of solid tumours). Mostly single lesions, if they are localized in the rib, fluoroscopy is helpful.

Clinical Importance: Typical pleural plaques indicate that, the person has been exposed to asbestos fibres (8) and that, sufficient time has elapsed since the first exposure to increase the risk of malignancy (6). For this reason it has been recommended that affected persons should be followed-up closely.

Pleural plaques are generally considered benign lesions and most authors strongly believe that they are not precursors of malignancy. However, early malignancy has been detected in pleural plaques (12). Furthermore they are fairly common in patients with asbestos related malignancies (3, 8, 13).

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PLEURAL THICKENING

Visceral pleural thickening is the most common disease seen in asbestos workers and it is nearly always associated with subpleural parenchymal fibrosis. These two changes explain the "Shaggy heart" and "unsharp diaphragms" which are the signs of visceral pleural thickening caused by asbestos inhalation (2, 4). Pleural thickening sometimes appears as interlobar fissural prominence (5).

In most cases, other asbestos related diseases accompany the pleural reaction. The disease can be progressive and may lead to restrictive respiratory failure sometimes severe enough to require decortication.

Other complications of pleural thickening are development of mesothelioma (1), deformation of the pleura which may cause alteration of bronchial anatomy, atelectasis and "pseudotumours" (2, 3, 6). In the plain chest x-ray, atelectasis, induced by asbestos related pleural thickening is easily misinterpreted as malignant lesions. CT scan may show its relation to the thickened pleura.

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ASBESTOS - RELATED DISEASE IN TURKEY

- ASBESTOS IN TURKEY: MINES, DEPOSITS, PRODUCTION USES AND HISTORY OF ASBESTOS - RELATED DISEASES
- MİHALIÇÇIK/ESKİŞEHİR SURVEY
- HACIHASAN - ILGAZ/ÇANKIRI SURVEY
- GARİPLER - SORGUN/YOZGAT SURVEY
- EREĞLİ/KONYA SURVEY
- ÇEVRELİ - ALMUS/TOKAT SURVEY
- BEDİRLİ - YEŞİLOVA/BURDUR SURVEY
- SOUTHEASTERN ANATOLIA SURVEY
- GÜRPINAR - ŞABANÖZÜ/ÇANKIRI SURVEY
- SARIKAYA - ÇEKEREK/YOZGAT SURVEY
- DISCUSSION ON 160 CASES OF MALIGNANT PLEURAL MESOTHELIOMA COLLECTED FROM ASBESTOS VILLAGES
- CLINICAL EVALUATION OF 13 CHRONIC FIBROUS PLEURISY COLLECTED FROM ASBESTOS VILLAGES
- MALIGNANT DISEASES AND PLEURAL ASBESTOSIS
- SUGGESTED PREVENTIVE MEASURES FOR ASBESTOS VILLAGES

ASBESTOS IN TURKEY

Mines, Deposits, Production and Uses

It is not yet clear whether the ancient civilizations who lived in Turkey knew about the asbestos ores, but they were first discovered in the Mihalliccik district of Eskişehir in 1921.

From the records available, up to 1969 asbestos production in Turkey was 3.748 short tones (1 short ton = 907 kg) per annum. This is used for roofing material and other building materials, pipes, asbestos, cement, brake lining, and paper manufacture. Since the amount of asbestos produced is insufficient to meet all the country's requirements, large quantities are purchased mostly from Canada, South Africa and USSR. Available information concerning asbestos deposits, indicates that Turkey has the potential to be self sufficient in the future.

For many years, asbestos production in Turkey has been carried out by private individuals and companies. The most important of these are Turkish Asbestos Mining and Commerce Company Ltd., Çanakkale Ceramics Company, Özgür Atermit S.T. Adana; Oralitsa İnş. Malz.S.T. Istanbul; Superlit Elyafli Çimento S.T. Istanbul; Doğusan Boru S.T., Erzincan; Mardin Asbest Boru S.T., Mardin; Eternit S. Istanbul; Asbest Endüstri, Istanbul; As-Ka Balatacilik O.S.T., Istanbul; are the companies use asbestos to manufacture various products.

The known large mineral deposits in Turkey are in Antakya, Sivas, Erzincan, Bursa and Eskişehir regions. Additionally, there are smaller deposits in İzmir, Çanakkale, Konya, Adana, Ağrı, Çorum, Çankırı and Ankara. Some of the specific locations are*:

Adana Region: Kaypak-Osmaniye; Gelincik-Haruniye, Gerdibi and Meydankoyu-Karsanti.

Ankara Region: Beynam source-Balâ.

Ağrı Region: Kumdere-Molla Ali/Cumaçay.

Aydın Region: Kızılkaya-Koçarlı; Atlamaç Köprüsü-Dağyeni/Germencik; Kızılışık Village-Yarıkkaya.

* From: Ulusu, E., and Yılmaz, S.: Türkiye'de Asbest Envanteri. MTA Enst. Yayınları, No. 157, MTA Enst. Matbaası, Ankara, 1975.

Balıkesir Region: Rahmi Mezrası, Kaleyanı-Erdek; Örencik Cami-Dursunbey/ Gökçedağ.

Bilecik Region: Dereyürük, Pamuklu, Çele, Bağıllar and Güneyköy occurrences in Osmaneli district.

Bursa Region: Dombayuctu, Terca, Purhassalik, Ortadere, Kumlugedik, Sülüklü, Topukköy, Göynükbelen, Dönmeler, Candır Deresi in Orhaneli district. Kırıklık-Kuruçeşme in Inegol district. Meskure and Karataş in Yenişehir district.

Çanakkale Region: Pınaroba-Intepe, Yapıderesi, Arıkanat, Kilise Tepesi-Biga, Tepecik-Beyçayırı/Lapseki; Çamlıkaltı-Sezak/Yenice.

Çankırı Region: Gümerdeğin, Gökdere, Akkaya, Gürpınar-Şabanözü.

Çorum Region: Alancı-Mecitözü.

Denizli Region: Bunar, Alan, Erenler, Alisar, Elembey, Bekili-Çal.

Eskişehir Region: Kurudere. Pataklı, Büyükler, Uludere, Maden, Kınıkdere, Davulkaya-Karakaya occurences in Central District. Değirmendere, Kuplu Deresi, Curuk Cevizler. Gökdere, Yukarı Eygazi, Samançukuru, Tepelce, Ayvalıca Doruğu, Çakmaklıpede, Taşköprü Pınarı, Yukarıalan, Zortaş, Kayayayla, Hamzaoğlu Deresi, Kırbız Dağı, Karakaya, Meydanlı, Kirazlı, Kadın Öldüren, Dereiçi, Kepen, Ardıç, Akbayır, Cevizlidere, Gökçeöz, Karağac, Tombakkaya, Yuvalca, Kekkaya, Suludere, Çakmaklık, Güvemtepesi, Kermeli Çayı, Övezderesi, Öğez Kası, Kelbesi Çayı, Kelbesi, Tatarcık, Kayı, Karacaören, İncirli and Suludere in Mıhallıççık District.

Hakkari Region: Begezvi Yaylası and Mehendi Deresi - Nugaylan/Şemdinli.

Hatay Region: Gökyar, Kalıncık, Kurudere, Fellahın Mezarı, Fehminin Yolu, Kamışlıpınar, Sümberikarlığı, Kise Çayı, İncirlipınar, Olukpınar in Kızıldağ District.

İzmir Region: Karateke-Tire

Kars Region: Kavalık-Aktaş/Kağızman; Tandırlar, Mermer Dağı, Mağara-Aktaş/ Kağızman.

Kastamonu Region: Gökbelen, Yeniköy-Taşköprü.

Kayseri Region: Bünyan and Pınarbaşı District.

Konya Region: Dereköyü/Konya Central; Kildere-Karaoğlan/Bozkur; Maydos, Dutlu-Zıvarık/Cihanbeyli.

Malatya Region: Deveci Köyü-Hasançelebi/Hekimhan; Gündüzbey-Yeşilyurt.

Muğla Region: Armutalan-Kozağacı/Muğla Central, Selimiye-Bozburun/Marmaris, Emecik-Datca.

Niğde Region: Deliyayla - Kılankoyu/Ulukışla.

Sakarya Region: Kuzuluk-Akyazı.

Sinop Region: Kızıloğlan - Boyabat.

Sivas Region: Citmederesi, Susuz Köy-Hamo/Divriği; Hüseyin Tepe, Göktaş-Kavak/Kangal; Ateş Ali, Davutyayla, Karataş, Acıyayla - Zara.

Tekirdağ Region: Kızılcaterzi-Şarköy.

Tokat Region: Sarıcam Deresi, Zile Bağları -Zile.

Trabzon Region: Hoca Burnu - Dağbaşı/Sürmene.

Tunceli Region: Kurt Tepesi-Dereova/Nazimiye.

Uşak Region: Eldeniz, Katrancamıaltı, Madenlik, Taşburun, Banaz.

The types of asbestos found in most of the regions mentioned above are either chrysotile or amphibole, most of which have no economic value.

Our studies have revealed other uses and methods of exposure to asbestos, that are very important in environmental health. This related particularly to the high incidence of asbestos associated lung disease which results from a number of different applications of asbestos mixed white soils in some of the Central Anatolia's villages.

The main uses of asbestos containing solis are:

1. *Whitewash or plaster material.*
2. *Substitute for baby powder.*
3. *In the preparation of grape juice and wine.*
4. *On roofs for insulation and prevention of leakage.*
5. *The production of earthenware and ceramic pots.*
6. *Cleaning of teeth.*

The full extent of the consequences of asbestos exposure will be discussed in the ensuing pages.

HISTORY OF ASBESTOS - RELATED DISEASE

The first scientific study on mesothelioma was done by Hamdi Suat and his associates between 1917-1929 and they suggested the term "Coelothelioma" for the disease (22). Later on, many case reports on mesothelioma appeared in Turkish Medical Journals (1-3, 6, 16, 19-21, 24). Köksal (22) published the results of his experimental research on pleural and pericardial mesothelioma and Yalav and Öktem, the results of their clinical research on mesothelioma (25). Fıratlı, Ersevim and Şen (17), presented also some cases they referred to as pleura-broncho-pulmonary malignancies at a national congress.

The first epidemiological survey on mesothelioma and its relation to asbestos, in Turkey, was done by the Chest Disease Department, Hacettepe University School of Medicine, Ankara in the Mihalliccik region and Asbestos mills in Sivas in 1973 and the results were presented at the 11th Turkish Tuberculosis Congress held in Bursa in the same year (18). The results of these and subsequent studies were published in Turkish and later in other international journals (4, 5, 7-15, 23).

Similar field studies were done by Yazıcıoğlu (26, 28) for his thesis in 1973-1974 and the results were later published.

Two different fibrous minerals are responsible for the endemic pleural diseases in Turkey-namely, asbestos and fibrous zeolite (Fig. 2).

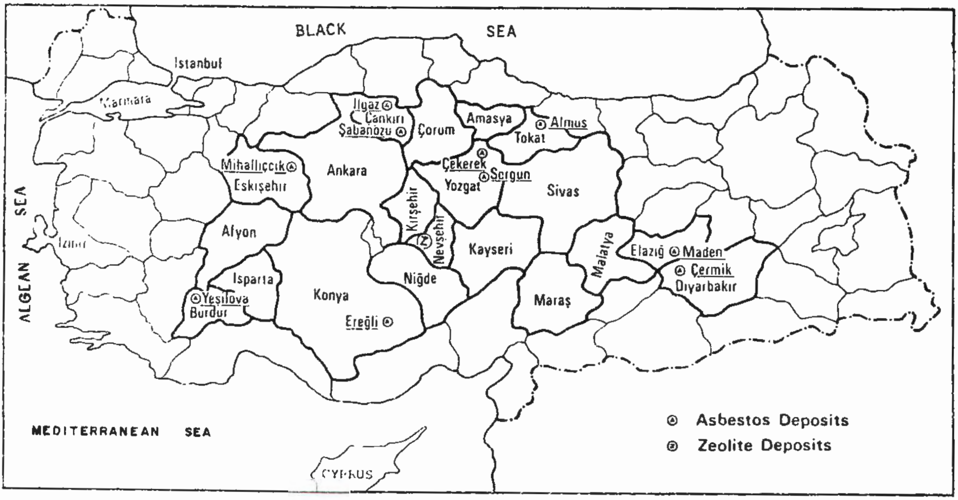

Figure 2. Map of Turkey showing areas with endemic asbestos and fibrous zeolite related diseases.

The results of the study done by the Department of Chest Disease, Hacettepe University, School of Medicine in the rural areas of Anatolia will be presented and discussed.

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MIHALLIÇÇIK/ESKİŞEHIR SURVEY

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The geologic map of Turkey shows that there are many asbestos deposits in the Mıhallıççık area. We were informed that, besides asbestos mines, there are some asbestos mills and factories in the town centre. A team consisting of chest physicians, a geologist and a mineralogist conducted the field survey.

The initial information taken from the attorney general of the district was interesting. He mentioned that, on autopsies done for legal cases, there were stony lesions covering the lungs. A picture he had never previously seen in his extensive travels in Turkey.

We evaluated some standard chest x-rays taken at the Tuberculosis Control Dispensary and noticed typical asbestos related calcifications and pleural thickening on some of them. These cases were labelled as tuberculous calcification in the dispensary.

Environmental Study:

Mihallıççık is a town in the district of Eskişehir. The town and the district are rich in asbestos, chromium, kaolin, marble, clay and sepiolite. There are many workshops, mills and factories in the town.

The town was dusty, especially during the day when the mine and mills are functioning. Residents of Mıhallıççık, once complained to the town authorities about air pollution and they asked for the removal of these workshops to an area outside the town.

On the outskirts of Mihallıççık, there were many open asbestos mines. From there, the ore was extracted with spades and shovels and moved to the depots in the town.

We saw many deposits of white soil and we were informed by the villagers that they use this as whitewash or plaster material, substitute for baby powder, and in the preparation of grape juice or wine. The whitish-grey soil is also used on roofs for insulation and prevention of leakage and for the production of ceramic pots and earthenware.

There is a chromium mine in the district and most of the workers are from nearby villages.

Those who work either in small open mines, workshops, mills or in the factories can easily carry mixed dust to their homes.

Geological and mineralogical study in the environment of Mihallıççık, showed thin, thick, short and even long tremolite fibres, chrysotile, actinolite and anthophyllite types of asbestos along with other clay minerals.

Geological and minerological studies of different white soils from local sources showed that some of them contained only talc, mica and clay minerals, but not asbestos For example, the white soil obtained from Gökdere village nearby, contains long tremolite fibres and is also used in Kayı (Yaka Kayı) and Kızılcaören villages. On the other hand, the soil taken from Alpu, has no asbestos fibres at all and is used by nearly all the villages located south of Mihallıççık district.

The information from the environmental studies indicate that, people from Mihallıççık district start to inhale asbestos mixed dust right at the beginning of their lives. It is thus expected that asbestos related diseases will occur in them at an earlier age.

Radiological Screening:

Microfilms of more than 50 villages in Mihallıççık district, were obtained from the General Directorate of the National Association against Tuberculosis, Ministry of Health and Social Affairs. These 70X70 mm microfilms were re-examined from the point of view of asbestos related chest diseases.

Table 11 shows our radiological findings in some villages that had a high percentage of calcified plaques:

No calcified pleural plaques were foud in Karaçam, Akgüney, Mahmuthisar and Ahırkoy.

We did not detect any malignant pleural disease, but pleural thickening was found in 10 percent of cases.

Case Control Studies:

The department collected 255 cases of malignant pleural mesothelioma in 1980. 160 were from asbestos villages and 6 of these cases were from the Mihallıççık district.

We admitted 2 cases of diffuse lung fibrosis from Mihallıççık, who had been working for a long time in the asbestos mills and who initially were treated as pulmonary

Table 11. **Villages where a high proportion of typical calcified pleural plaques was found in the 70 × 70 mm microfilm.**

Name	Number of microfilms	Patients		Calcified Plaques%	Average Age
		Male	Female		
Mihallıççık	3880	217	180	10	55
Sorgun	541	27	24	9.6	62
Çardak	317	14	8	7	59
Gözeler	213	8	7	6.5	58
Güres	269	10	5	6.3	55
Seki	440	14	8	5.6	61
Kavak	1677	55	29	5	58

tuberculosis due to upper lobe lesions. Physical examination revealed fine crepitations and clubbing. Their chest x-rays showed, diffuse apical fibrosis with cystic changes and bilateral diaphragmatic calcified plaques. Their sputum was negative for acid-fast bacilli. They were diagnosed as atypical asbestotic fibrosis.

Fig. 3 shows chest x-ray of a patient from Mihallıççık. He was also admitted to the Hacettepe University Hospital for further evaluation. He was diagnosed as asbestos pleural effusion and pleural thickening, calcified pleural plaques, and lung fibrosis were found clinically and histologically. He was followed-up for more than 5 years without any change.

Malignant pleural mesothelioma was diagnosed in a 33-year-old female patient who spent her childhood in Kaya (Yaka Kayı) village. The diagnosis was established by closed biopsy. Glucose level in the bloody effusion was once found to be very low and at that time she presented with a manic reaction on the ward. We followed this patient for more than 6 months and terminally she developed Horner's syndrome. Typical calcified pleural plaques were detected in her father's microfilm.

Comments

Environmental studies have revealed that there are both chrysotile and amphibole type asbestos in the district. Occupational, paraoccupational and environmental exposure to asbestos is always possible. Screening of microfilms show that there is a high percentage of benign asbestos related pleural disease. These diseases are more in the village where asbestos mixed white stucco are used. It is difficult to comment on the incidence of asbestos related lung fibrosis by looking at microfilms, but we believe that if standard chest x-rays were available, the incidence of pleural asbestosis, that is, calcified and hyalinized pleural plaques and pleural thickening would be more and would enable us comment on pulmonary asbestosis.

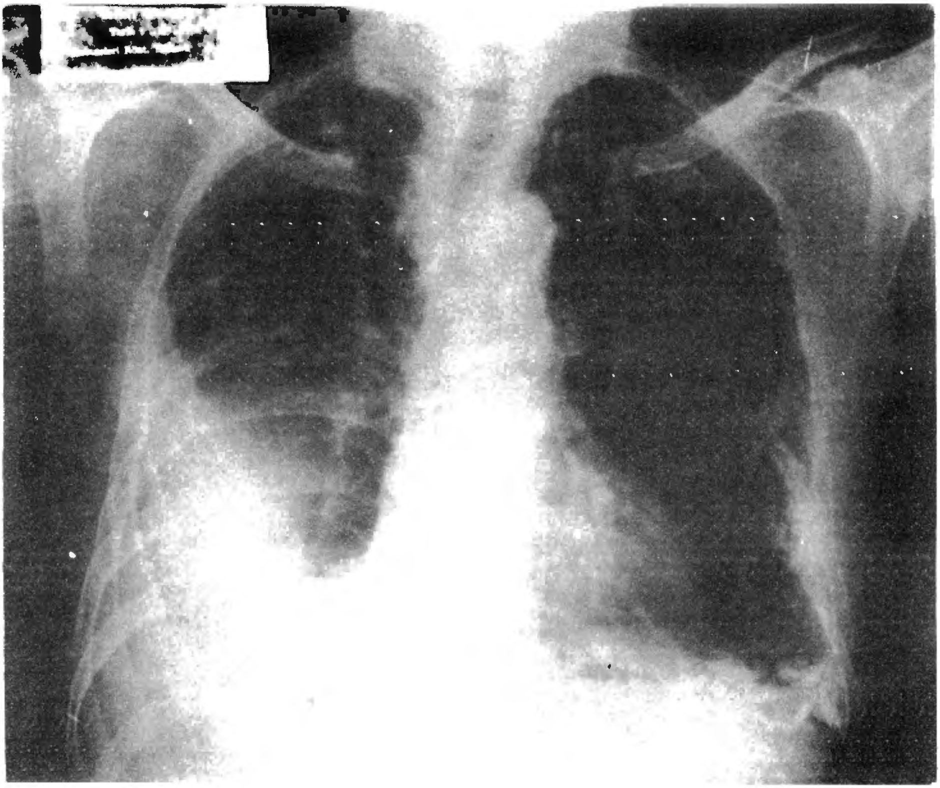

Figure 3. Typical bilateral calcified pleural plaques with right sided pleural effusion and left sided pleural thickening: Case from Mihallıççık, an asbestos town.

The percentage of calcified pleural plaques is high in some villages. This might be related to the intensity of inhaled asbestos dust, the type of asbestos and the dimensions of fibres.

Most of the patients were above 50 years of age. Environmental studies definitely suggest that the inhibitants of Mihallıccık district have been exposed to asbestos dust since their birth. We expected the pleural diseases to occur in younger persons and our youngest patient was a 19 years old male. It is well known that when a patient gets older, the amount and density of calcification becomes more prominent. If we had used conventional chest x-ray in our survey, the average age of our cases would have been lower.

Considering the general incidence of mesothelioma, the 6 cases of pleural mesothelioma found in the Mihallıççık region is significant. Mineralogic studies done in the

Institute of Mineralogic Research and Exploitation, demonstrated that there are thin and long tremolite fibres in the Gökdere village. These types of fibres easily induce mesothelioma. The female patient mentioned earlier is also interesting. She must have inhaled asbestos fibres very early in life. Her father also must have been exposed to the same fibres, since they shared the same environment. Why she had mesothelioma and her father had calcified pleural plaques is uncertain. It is possible that cellular and humural immune-mechanisms might play a role here.

HACIHASAN - ILGAZ/ÇANKIRI SURVEY

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There were a 13 cases of pleural mesothelioma from Çankırı district. We re-examined the 70 X 70 mm microfilms of the inhibitants of this region, taken previously by the mobile microfilm units of the Directorate of Tuberculosis control. A high proportion of calcified pleural plaques were detected especially in the villages of Hacıhasan and Beyköy. We thus carried out subsequent research studies in Hacihasan over a three year period.

Environmental Study:

The population of Hacıhasan village was 750 and it was located near the forest. The main income of the villagers was from either forest products or from harvesting agricultural goods. Most of the houses were made from wood and mudbrick, and the walls were plastered with mud. They rarely used white stucco to paint the walls.

The Hacıhasan dwellers obtained their water from the Bartı spring source just behind the village. There is no asbestos mill, worshop or factory in here. Geological samples were taken from street soils, rocks and roof soils. Airborne dust samples were taken with a Casella type air dust apparatus and examined by both optical contrast microscope and electron microscope after crushing and dispersing in water with ultrasonic vibrations and filtering through a membrane filter.

Respirable and total environmental dust samples obtained with the Casella type dust sampler were evaluated with optical contrast microscope.

Water samples were collected from two sources and analyzed at the Physics Department of Ankara University for the presence of fibres.

Environmental study revealed that there were tremolite type asbestos together with mica and calcite. Air dust filter analysis also showed tremolite fibres, calcite, chlorite, eckermannite, mica, rutile and zeolite.

Analysis of water samples collected from Bartı springs, revealed numerous asbestiform fibres in the sediment.

Epidemiological studies:

70X 70 mm microfilm were re-examined from the point of view of asbestos related diseases. The results are shown in Table 12.

Table 12. Microfilms results of Hacihasan and other villages in Ilgaz District.

Name of village	Number of microfilm	Number of patients	Calcified plaques %
Hacıhasan	285	15	5.2
Beyköy	95	5	5.2
Sazak	87	2	2.2
Musa	118	1	0.8
Yerköy	270	2	0.7
Arpayeri	137	1	0.7
Kurmalılar	179	1	0.5
Cendere	193	0	0
Bükcük	135	0	0
Inköy	93	0	0
Kale	283	0	0
Onaç	121	0	0

Clinical examination together with standard chest x-ray screening were done in 160 villagers aged over 25 years in Hacıhasan. Typical pleural calcification was found in 20 percent and pleural thickening in 22 percent of the population. No malignant diseases were detected.

Case control study was also carried out in the village. From 1978-1980, 13 persons died from malignancies (8 male, 4 female). Of these 7 had gastric carcinoma and one each of lung, laryngeal, urinary system, liver, esophageal cancer and leukemia.

Comments

Mass microfilm screening had suggested that, Hacıhasan dwellers must have inhaled fibrous mineral, either asbestos or others. The percentage of calcified pleural plaques increased by 20 percent with standard chest x-ray screening. Hacıhasan is a village near a forest and there is no obvious air pollution. Cendere and Bükcük villages are only 1-3 km away from the Hacıhasan and their living conditions are not different. They are farmers and they also work on forest products and share the same fields. The only important difference is presumably their water source. They do not use Bartı spring water.

Environmental studies showed some fibrous minerals, mainly tremolite asbestos, mica, rutile and other clay minerals. Water analysis also revealed some asbestiform minerals. The villagers wash their clothes in Bartı water and if the responsible mineral is from the water, it may enter the body either by ingestion or by inhalation from the clothes contaminated during washing.

The white stucco in the village does not seem to be the source of fibrous minerals since only few people have used it in the past. Furthermore, the patients with the calcified pleural plaques never used white stucco.

The high incidence of calcified pleural plaques in the Hacıhasan village cannot be explained solely on the findings of fibrous minerals in the air samples because the surrounding villages although they share the same environment, their inhabitants do not have pleural plaques. The spring water is thus the most likely source of the mineral fibres.

The other interesting finding in Hacıhasan village is the high incidence of gastrointestinal malignancies. We are aware that the incidence of digestive system cancer, mainly esophageal and gastric malignancies is more than 3 times as common in asbestos workers.

The results of our epidemiological case control studies do not adequately explain the high incidence of benign asbestos related pleural disease and gastrointestinal cancers. More detailed epidemiological studies together with mineralogical investigastions in the tissues would be helpful to explain their health problem.

GARİPLER - SORGUN/YOZGAT SURVEY

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More than 20 cases of malignant pleural mesothelioma were collected from Yozgat and its surrounding areas. Fourteen of these cases came from the Sorgun District and 5 of them were from the village of Garipler.

The Geological map of Turkey shows that there are many asbestos deposits and occurences in Yozgat and the areas around it.

These were the main reasons why we carried out our studies in Garipler village.

Environmental Study:

Garipler village was essentially founded by Anatolian Greeks. About 50 years ago, after the establishment of new Turkey, the Greeks migrated to Theselanico. A group of Turks from the Kırımsen village of Theselanico then moved to Central Anatolia and settled in Garipler because of its large water supply.

The population of the village was 500 in 1970, but it had decreased by 1975, to only 163 people, 76 men and 87 women. Most of the villagers had moved into the cities of Sorgun and Ankara in search of better ways of earning a living. Those who migrated took jobs in transportation and house construction.

There was no asbestos mine, mill or factory in the village. Most of the houses were built by the Anatolian Greeks and their walls were constructed with hard reddish rocks which were collected from a local quarry. The roofs were covered with grey-bluish earth and clay. The walls of the houses were plastered with white stucco called "Ağcın soil" because it was collected from the nearby village of Ağcın. The white soil was also used as grape molasses, earth and baby powder.

Geological samples were taken from the houses of the patients with mesothelioma, and from the original source of the white stucco.

Respirable and total environmental dust were also collected by a Casella type machine from the homes of the patients with mesothelioma.

Samples were evaluated with optical and electron microscopy and the composition of the fibers was analyzed with EDAX in conjunction with transmission electron microscopy.

The analysis of the geological samples using optical microscopic and x-ray diffraction methods revealed a calcite, quartz-feldspar and serpentine. However, examination of air filters showed many chrysotile and rare tremolite fibres. The size of the fibres were less than 1 micron in diameter, but more than 10 micron in length.

Case Control Study:

Since there were few people over 25 years in the village, an epidemiological survey was not carried out. However, by establishing regular and close contact with the villagers who were in Garipler and other areas, some patients were picked up and were examined at the Hacettepe University Hospital.

We saw 5 cases of malignant pleural mesotheliomas, 3 of benign asbestos-related pleural disease (pleural asbestosis), 2 of gastric cancer, 2 of cancer of the urinary system and cancer of the rectum in a 13-year-old boy.

Our first two patients with definite pleural mesothelioma were a 45-year-old male and his 43-year-old brother. They were both born and raised in Garipler village.

The parents of one of the affected families (the Sungur family) were born and brought up in Kırımsen-Theselanico and came to Garipler as a young married couple who had and raised all their 4 children in the village. The father was killed in a fight, but the mother died at the age of 65 years from pleural mesothelioma. A daughter died of the same disease earlier than her mother at the age of 33 and the youngest of the brothers was found to have malignant mesothelioma in the hospital. Chest x-ray in an elder brother who was complaining of dull chest pain revealed hyalinized and calcified pleural plaques. Thoracoscopy and biopsy ruled out mesothelioma and revealed only fibrosis. Typical pleural calcification was seen in the chest x-ray of the eldest brother. Fig. 4 shows the family tree of the Sungur family.

Comment

In Garipler village, with a population of only 500, there is an excessive number of malignant and benign mineral fibre-related disease. Although we do not have any mineralogical studies in the lung tissues, environmental studies strongly suggest that the cause is most probably asbestos. The sizes of chrysotile and tremolite asbestos is optimal for the induction of the diseases that we encountered in the village.

The three cases of malignant mesothelioma in the same family can be explained on the basis that the family members inhaled the same atmosphere. However, a familial predisposing factor such as an immunological defect enhancing the development of the disease should also be considered.

The survey of Garipler village also demonstrated the relation between the latent period between the time of exposure and the development of asbestos related disease. Asbestos related disease was detected in patients aged over 65 years who were born and brought up in Greece. In contrast however, these diseases were detected at a younger age in those who were born and brought up in Garipler.

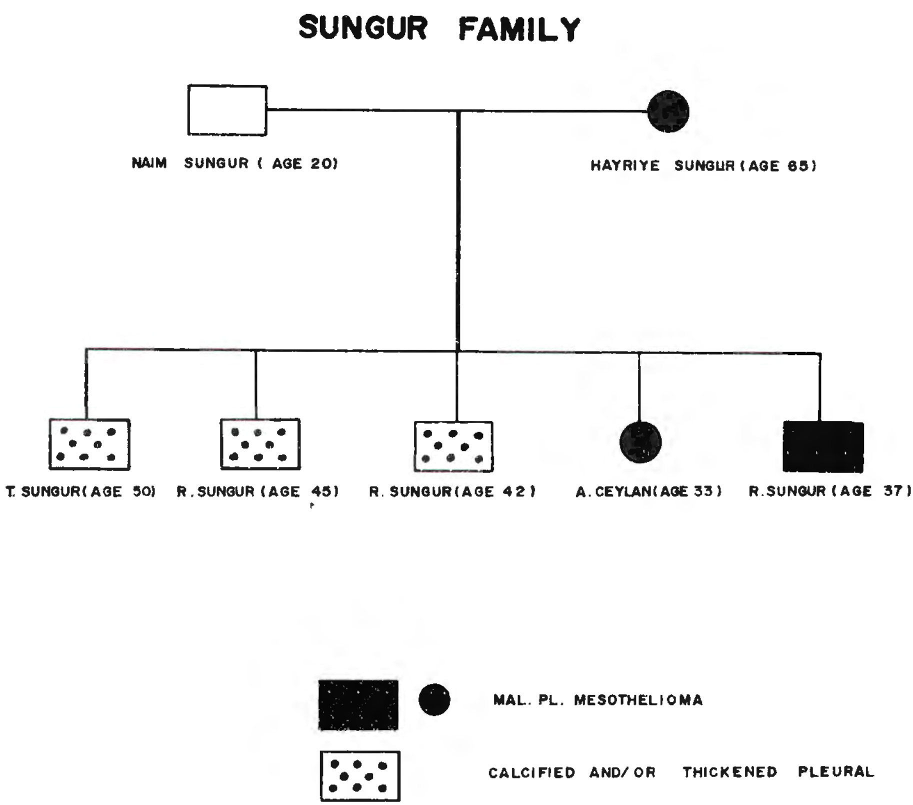

Figure 4. Pedigree of the Sungur family from Garipler village.

EREĞLİ/KONYA SURVEY

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We collected 14 cases of mesothelioma from the villages of Ereğli district of Konya. Most of these patients were peasants and they came from Halkapınar, Orzala and İvriz villages. The observations that there were many deposits of asbestos in the same region encouraged us to study that area.

Environmental Study:

The villages were located in the valleys of the Toros mountains and their main income was derived from agriculture and live stock breeding. There have never been any asbestos mines, mills, depots or factories in the villages or sorrounding areas. However, the inhabitants of Halkapınar stated that soft mineral (asbestos ?, Clay ?) had been found in the mountains but this has never been used. They had also observed that after heavy rains, the streets of Halkapınar were covered in a white mud coming from the mountains.

Many geological samples were collected from suspected materials and white soils that the villagers had used in the past but only some of the white soil showed tremolite type asbestos. Dust sampling was not carried out in the air.

Radiological Screening:

The 70 X 70 chest microfilms taken previously by the Mobile team of Tuberculous Control were re-assessed from the point of view of asbestos-related chest diseases. The results are shown in Table 13.

Table 13. Radiological Findings on Mass Survey with 70 × 70 mm. Films in Some Villages of Eregli/Konya

Name of Villages	Number of Films	Number and % of patients with Calcified Plaques
Eskihisar	600	36 (6)
Halkapınar (Zanapa)	2,000	64 (3.2)
Kuyusaray	250	8 (3.2)
Kusere	300	9 (3)
İvriz (Aydınkent)	600	16 (2.6)
Orhaniye	150	3 (2)
Karayusuf	400	7 (1.7)
Guylu	600	9 (1.5)
Yıldızlı	300	4 (1.3)
Dedeli	500	6 (1.2)
Gökceyazı	627	5 (0.7)
Yayıklar	440	2 (0.4)
Bulgurluk	400	1 (0.2)
Belceağaç	175	0
Çakıllar	150	0

Pleural thickening was also observed in most of patients who had calcified pleural plaques in the films.

We collected 12 cases of mesothelioma from the villages of Ereğli. Most of them had been admitted to the local hospitals and their initial diagnosis was tuberculous pleural effusion, but had not benefited from anti-tuberculous therapy. Some of their chest x-rays revealed typical pleural calcification and we made a provisional diagnosis of mesothelioma.

We also screened radiologically other family members of the patients and found pleural asbestosis in some of them.

Comment

This preliminary study shows that there is definitely mineral fibre related disease in the Eregli region. Konya is a large area, but almost all cases of mesothelioma from the region are scattered in the district of Ereğli. There is localized, endemic pulmonary and perhaps extra-pulmonary disease in the area. Our initial environmental study suggested that the etiology of these diseases is most probably asbestos.

We are planning to do epidemiological and more detailed environmental study in the Ereğli region.

ÇEVRELİ - ALMUS/TOKAT SURVEY

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** *MRC. Pneumoconiosis Unit, Llandough Hospital, S. Glamorgan, U.K.*

We collected 8 cases of malignant mesothelioma from the villages of Tokat area, namely Almus, Turhal and Erbaa districts.

The geological map of Turkey shows that there are lots of asbestos deposits in that area.

We admitted a case of chronic pleural effusion in a 48-year-old male patient from Çevreli village of Almus District and although 3 consecutive pleural needle biopsies did not show any malignant disease, a tumoural mass located at the biopsy site strongly suggested a malignant pleural disease. The son of the patient was a conscientious and observant school teacher and he stated that his uncle also died 6 months earlier from lung disease.

Based on the above evidence, we decided to do further studies in this area.

Environmental Study:

Çevreli village was located in a forest area around the Almus Dam. It's older name was Mohat. The main sources of income of the inhabitants were forestry, agriculture, and live stock breeding and some of the young females wove carpets. The houses were made from wood or mudbricks and plastered with a greyish-white soil obtained from deposit of Sofutas are located 5 km. away from the village. Some of the roofs of the houses were also covered with the same soil.

Geological samples were taken from suspected areas and the Sofutaş source.

Respirable and total environmental dust were collected by a Casella type pump from the streets and from the Sofutaş source after dusting.

Samples were evaluated with optical and electron microscopy and the composition of the fibers was analyzed with EDAX in conjunction with transmission electron microscopy.

Mineralogical examination of geological samples obtained from the village is shown in table 14.

Table 14. Mineralogical results of samples from Çevreli village

Name of Sample	Mineralogical Composition
White earth 1	Calcite, amphibole, chlorite
White earth 2	Mica, quartz, amphibole, chlorite
White earth 3	Mica, chlorite quartz, feldspar
Göze region earth	Mica, feldspar, chlorite
Roof earth	Talc, serpentine
Earth from meran field	Chlorite, amphibole, feldspar
Sofutaş source	Serpentine, talc and calcite

Analysis of air filter content showed chrysotile, tremolite asbestos fibres in addition to rutile, kaolin, talc, mica and small amounts of iron and calcium carbonate.

Epidemiological Study:

A questionnaire consisting of the personal identification name, age, sex, duration of stay in the village, smoking habits, past and family history, use and source of white stucco, positive physical findings, and radiological results was filled for each subject over 25 years old.

A total of 180 villagers were examined and screened with standard chest x-ray. Nineteen films were discarded due to their poor quality. Of the 161 subjects studied, there were 84 women and 77 men. The average age of the women was 41, and that of the men was 46 years.

Abnormal findings detected from the 161 villagers is shown in Table 15.

The average age of the patients in whom both calcified pleural plaques and pleural thickening were present was 51 years in females and 55 years in males.

We also re-assessed the 70 mm X 70 mm films taken in 1971 and results are shown in table 16.

Case Control Study:

As mentioned earlier there was only one case of malignant mesothelioma from Çevreli village. We kept close contact with the villagers for more than 5 years and could not find any additional case.

Table 15. **Abnormal radiological findings found in 161 persons over 25 years old in Çevreli village**

Abnormalities	Number and percentage
Calcified Pl. Plaques and thickening	8 (4.95)
Pleural thickening	6 (3.72)
Obliteration of c - d angles	6 (3.72)
Tuberculosis	5 (3.10)
Small opacities (fibrosis)	5 (3.10)
Pleural calcification	4 (2.48)
Bronchiectasis	4 (2.48)
Tumour ?	1 (0.60)

Table 16. **Radiological findings on mass survey with 70 × 70 mm films in Cevreli village**

Number of microfilms	1736
Pleural thickening	26
Obliteration of c-d angles	12
Pleural effusion	7
Tuberculosis	5
Pleural calcification	1
Tumour	1

One patient with extensive pleural thickening was admitted to the hospital for surgical management. Decortication was done and both pleural and lung samples were examined histopathologically and revealed tuberculosis.

Comment

Although, the environmental studies in the village showed asbestos, we had found only one case of mesothelioma. The incidence of calcified pleura was not as prominent when compared with those of other asbestos villages. Some of the radiological changes were most probably related to tuberculosis.

BEDİRLİ - YEŞİLOVA/BURDUR SURVEY

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We found 3 cases of chronic fibrosing pleuritis and one case of mesothelioma from Burdur.

The geological map of Turkey indicated that there was a lot of asbestos deposits, mainly of the serpentine type in this area.

We had been informed by Dr. Aytekin Erol, a radiologist in Burdur, that he had seen widespread pleural calcification in the chest x-rays of a patient from Bedirli village. (Fig. 5). This motivated us to continue our studies in Bedirli.

Environmental Study:

The population of Bedirli was 643 and their main occupation was agriculture and live stock breeding. The village was located on a slope and the houses were constructed from mudbrick, bricks, and wood. Most of the houses did not have sloping roofs, but a material called "Ceren Earth" was spread on the roofs. They also used white stucco for plastering and for other purposes.

Geological samples were taken from the origin of Ceren earth, white stucco, the streets and from small rocks.

Respirable and total air dust samples were taken from 3 houses using the Caselia type dust collector.

Samples were evaluated with optical and electron microscopy and the composition of the fibres was analyzed with EDAX in conjunction with transmission electron microscopy. The important results of the environmental survey were:

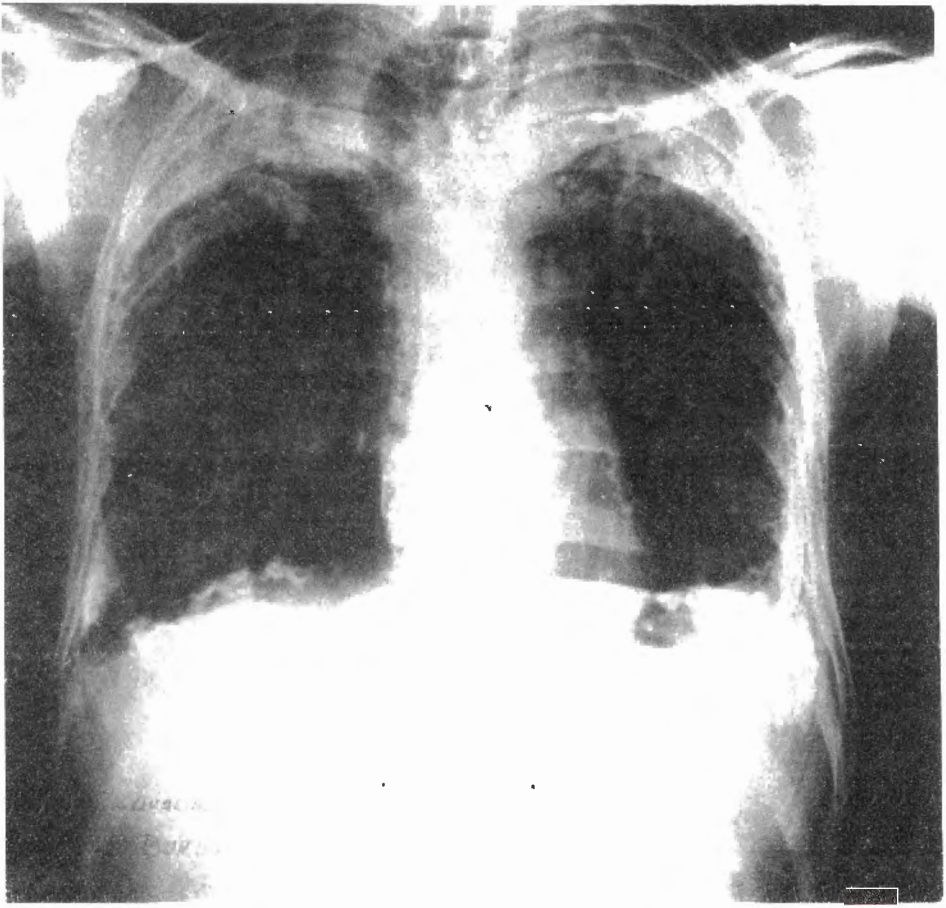

Figure 5. Typical bilateral extensive calcification with pleural thickening and apical pleural-parenchymal fibrosis: Case from an asbestos village in the Burdur area.

Geological samples: Chrysotile, tremolite, calcite, chlorite and clay minerals.

Air dust sampling

House 1: Chrysotile in the ratio of 86%, tremolite in the ratio of 21.5% and small quantities of zeolite and chlorite were found.

House 2: 90.2% of tremolite, 9.8% of dolomite, 5.3% chrysotile and traces of serpentine, calcium, iron, aluminium and silicate were found.

House 3: 72.6% of tremolite, 20.4% of chrysotile, and small quantities of calcite, chlorite and clay materials were found.

The count of fibres in filters of the first, second and third houses were 321.2×10^4, 264.2×10^4 and 152.5×10^4 respectively.

Epidemiological Study:

A questionnaire which included the items previously mentioned was filled for each individual. A brief clinical examination was done and standard chest x-ray taken on 199 people who were over 25 years old in the village.

There were 111 males and 88 females and the oldest patient was an 80 years old male. The average age was 44.3 years. Abnormal radiologic findings are shown in Table 17.

Table 17. The percentage of abnormal radiological findings in 199 persons from Bedirli village

Pleural calcification	24%
Pleural thickening	19%
Obliteration of costa-diaphragmatic angle	14%

Calcified pleural plaques seen in the chest x-rays were typical asbestos-related calcification. None of the patients with calcification gave a history of tuberculosis, haemothorax or empyema. Pleural thickening was mostly associated with pleural calcification.

Since chest x-rays were taken with portable machines, we could not comment on lung fibrosis.

Case Control Study

We found 3 cases of asbestos pleural effusion and one case of mesothelioma in Burdur area. Decortication was done in 2 out of 3 patients and the histologic findings confirmed the diagnosis. The last patient, a middle aged female, was treated conservatively.

Our surveillance of Bedirli village continued for more than 4 years. Two elderly patients who had calcified pleural plaques on their chest films died from gastric cancer. We did not detect any cases of pleural mesothelioma from Bedirli village.

Comment

The situation of Bedirli village was rather interesting. Environmental study showed the possibility of fibrous mineral, mainly chrysotile, tremolite asbestos, exposure and this was clearly seen in the chest x-rays.

The percentage of pleural asbestosis was quite high, but we did not find any malignant mesothelioma. The chemical and physical characteristics of inhaled mineral fibres are responsible for the occurence of these diseases.

We had an impression that the pleural diseases in the village are also encountered in other neighbouring villages to varying degrees.

SOUTHEASTERN ANATOLIAN SURVEY

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We saw a patient from Maden Copper Factory with typical pleural calcification. He informed us that most of the workers in the factory have similar changes in their lungs.

Yazıcıoğlu and his associates found calcified pleural plaques in the following proportions: 0.16% in Ergani, 3.7% in Cermik, 4.3% in Asağı Şeyhler and 14.2% in Yukarı Şeyhler. They also reported 162 cases of pleural and pulmonary malignancies in the region and stated that, pleural mesothelioma was 23 times and lung cancer 2.5 times more than in controls.

The geological map of Turkey confirms that there are many asbestos deposits in the Southeastern part of Turkey.

Environmental Study:

The area was very dry and dusty. Most of the houses were made from mudbrick and their roofs covered with whitish-grey soil. Both inside and outside of the houses were plastered with white stucco. Fig. 6 shows a house plastered with white stucco.

Mineralogic study done on the white stucco used locally showed mainly chrysotile and tremolite asbestos with some talc and other minerals.

Total air dust sampling was carried out with Casella type sampling apparatus on the streets of Maden, Yukarı, Şeyhler and Aşağı Şeyhler towns. The results were:

Maden: 97.5% of filter contained tremolite asbestos. There were also chloride and talc in small quantities.

Figure 6. A house in a village which is plastered with asbestos mixed white soil.

Yukarı Şeyhler: 35.3% tremolite, 25% chrysotile, 25% calcite and lesser amounts of zeolite, pyroxene, antigorite, chloride rutile and muscovite were also found.

Aşağı Şeyhler: 49.2% antigorite, 47.5% tremolite and small quantity of talc were found.

The diameter of tremolite fibres found varies between 0.125 to 1 micron, whereas their lengths varied between 1-6 microns.

Radiological Screening:

Standard chest x-rays were taken of 134 workers from Maden Copper Factory and assessed in relation to asbestos related chest diseases. Typical pleural calcification from asbestos was found in 2.4%, however, lung fibrosis with small opacities were more prominent and was present in nearly half of the workers. Most of those with pleural calcification were originally from the neighbouring villages. Fig. 7 shows a chest x-ray of one of the workers with calcification.

Case Control Study:

Among the 160 cases of pleural mesothelioma from the asbestos villages, 11 were from the Southeastern part of Turkey.

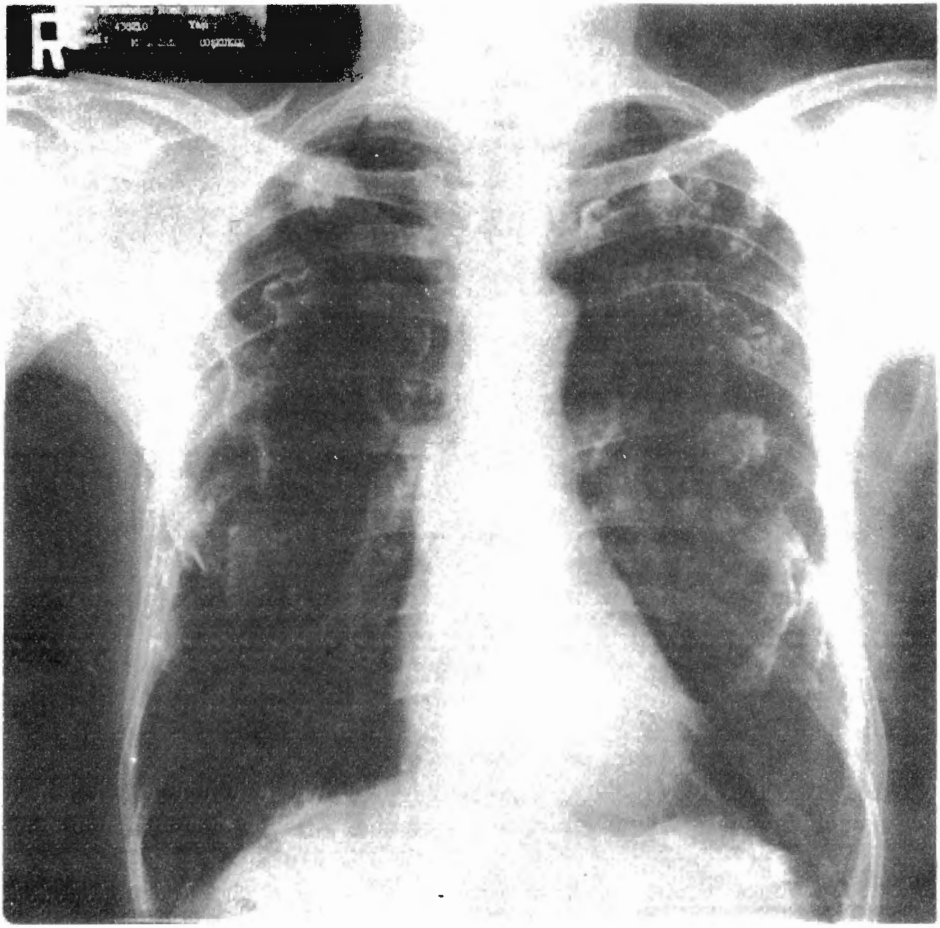

Figure 7. Extensive bilateral pleural diaphragmatic calcification: A case from Maden, an asbestos town.

They were all villagers and they had never worked in an asbestos mill, factory or mine at anytime. However, all of them lived in houses in which white stucco had been used. There were 4 females and 7 males and their age range was 40-60 years. They all gave a positive family history of the same type of illness.

Malignant mesothelioma was diagnosed in a 7-year-old female patient whose mother had also died from mesothelioma.

One of our patients from the same area had surgery for long standing pleural effusion. Histology of the tissues taken during decortication revealed granulomatous tissue reaction compatible with tuberculosis, diffuse fibrosis and some silicotic nodules. Mineralogical studies of the lung tissues was carried out with optical and electron microscopy and the number and composition of the fibres analyzed with EDAX in conjunction with transmission electron microscopy. These showed 80% tremolite asbestos, 14% aluminium silicate and mullite, 5.1% chrysotile and small amounts of rutile and iron oxide particles. Similar studies on another lung tissue of this patient showed 62% chrysotile, 34.7% tremolite and a small percentage of rutile, zeolite and crocidolite. In the first and second samples there were 73.5×10^5, 380.7×10^5 fibres, respectively in 1 gram of dried lung tissue. The diameter of the fibres ranged from 0.125 to 0.250 microns and their length from 1 to 8 microns.

Comment

Environmental study showed that there were many natural mineral fibres, namely, chrysotile, tremolite, mica, and antigorite and even zeolite. The inhabitants from the area inhale these fibers originating from the walls that have been plastered with white stucco.

Radiological screening and case control studies clearly demonstrated that in the southeastern part of Turkey, there were many villages with endemic pleural asbestos, malignant mesothelioma and fibrosis.

Mineralogic study done in one patient suggested that there may be mixed type pneumoconiosis in addition to common chronic lung infection. Although one cannot generalize that all patients in this area have mixed pneumonoconiosis, considering the dry weather and the composition of inhaled materials together with the clinical and radiological picture we are inclined to suspect a mixed type of dust exposure.

One can easily explain the endemic pleural asbestosis from the different types of asbestos fibres found in the area, but not so the high incidence of malignant disease. One possibility is exposure to optimal sized tremolite type asbestos.

GÜRPINAR - ŞABANÖZÜ/ÇANKIRI SURVEY

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From the Central Anatolia region, 160 cases of malignant pleural mesothelioma were seen from asbestos village and thirteen of these were from the villages of Çankırı district.

We had the opportunity to investigate one patient with diffuse lung disease from Gürpinar village. His chest x-ray showed diffuse lung fibrosis with small opacities scattered all over the lung fields together with linear calcification on the central part of diaphragm (Fig. 8). Histologic examination revealed lung fibrosis. Mineralogical examination of lung tissues showed 2×10^5 ferruginous bodies and 3×10^5 tremolite fibres per gram of dried lung tissue. The average length of fibres were 3.6 micron and their diameter was 0.23 micron. Silica and diatom particles were also seen in remarkable numbers in the tissue.

Environmental Study:

The village was located North of Şabanözü town, Its population was 1099 and the settlement depended on agriculture and livestock breeding for their living.

Most of the houses were made of brick, mudbrick and rocks. Those houses without sloping roof were covered with a grey-bluish earth, called "Çeren Earth".

The villagers plastered their walls with a white stucco obtained from the neighbouring village of Çapar Kayı. Thev found Çapar Kayı stucco better because it was more shiny than lime and once the walls are plastered with it, one did not need to whitewash over it with lime. However, some of the new houses were whitewashed with lime.

There was an asbestos mine just 1 km. from the village from where the mineral was extracted, loaded into sacks and taken to the village by animals and then transpor-

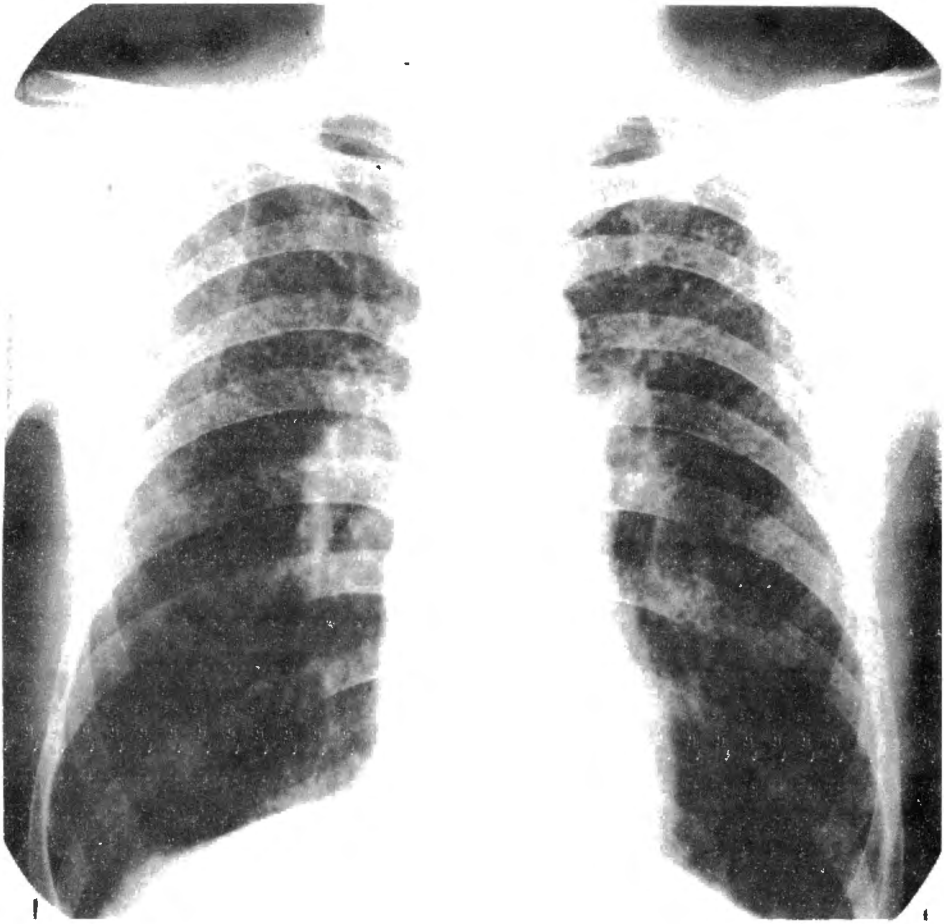

Figure 8. **Diffuse small opacities with fibrosis and right diaphragmatic calcification. A case from Gurpınar, and asbestos village.**

ted to Istanbul by trucks. It is reported that gaskets, brake lining and insulation materials were made from this ore. Most of the middle aged or older males worked in the mine for a short period of about 2-3 months. The mine work ceased 15 years ago.

Geological samples were taken from the dissused asbestos mine, the Çapar Kayı white soil and the earth used for grape molasses and for baby powder.

Air dust samples were taken, with Casella apparatus from the house of our patient with mixed pneumoconiosis, which was whitewashed by Çapar Kayı stucco and from the dissused mine and streets.

Mineralogical analysis of geological samples taken from the disused mine revealed serpentine, chrysotile and antigorite; the Capar Kayı white stucco was very rich in tremolite asbestos; the grape molases earth had limestones and tremolite eckermanite fibers in extremely small quantities; in the baby powder earth we found quartz, feldspar and mica.

Air filter analyses revealed between 4.7 to 5.1 fibres per ml. The fibres were more than 5 micron in length and between 2.9 to 7 fibres per ml air. All the fibres were tremolite asbestos.

Epidemiological Study:

There were 453 persons over the age of 25; 237 were male and 216 females. Using the stratified sampling method a total of 150 subjects (66 males, 84 females) were included in the study.

A questionnaire was completed for all of them, a brief examination was carried out and their peak flow measured with Wright flowmeter. Standard chest x-rays were taken with a Picker portable x-ray machine.

Out of the 150 subjects, 17 had pneumonia and 3 tuberculosis. The fathers of 12 had died of cancer and 20 people stated that there had been malignant disease in their families.

Thirty one males were smokers of 1 pack per day for a mean duration of 22.4 years.

Positive physical findings and radiological abnormalities are shown in table 18 and 19.

Table 18. Positive physical findings in 150 persons from Gürpınar village

Findings	Number and Percentage of Patients	
Coarse crepitation	45	30
Rhonchi	27	18
Fine crepitation	9	6
Barrel chest	5	3.33
Decreased air entry	4	2.66
Dullness	3	2
Chest deformity	3	2
Digital clubbing	2	1.33
Signs of mitral stenosis	2	1.33

Table 19. Abnormal radiologic findings encountered in the patients from Gürpinar.

Abnormality	Number and Percentage	
Calcified Pleural Plaques	22	(14.66)
Pleural Thickening	21	(14)
Pulmonary Fibrosis	21	(14)
Tuberculosis	7	(4.66)
Chest wall deformity	1	(0.66)

Case Control Study:

Our study in Gürpinar village continued for more than 4 years. During this period we followed-up 2 female patients, one with infected hydatid cyst in the lung and the other with gastric carcinoma. There was pleural thickening and fibrosis in the lung of the second patient.

Comment

There were endemic pleural calcification, chronic fibrosing pleuritis and lung fibrosis in the inhabitants of Gürpinar due to environmental inhalation of asbestos. Villagers were exposed to asbestos fibers most probably from the walls whitewashed with Çapar Kayı stucco. Since there were 4.7 to 5.1 asbestos fibres in 1 ml ambient air, one can calculate that people living in these houses would inhale more than 20,000 fibres in one minute. Although we did not find cases of mesothelioma,this did not mean that they were free of malignant disease since all the risk factors were available in the village.

SARIKAYA-ÇEKEREK/YOZGAT SURVEY

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There were scattered cases of malignant mesothelioma in the villages of Çekerek District. We diagnosed mesothelioma in a 35-year-old male patient from Sarıkaya village of Çekerek.

Environmental Survey:

There was no electricity or proper water supply in the village. The villagers derived a living from agriculture and livestock breeding.

The population of the village was 575; 273 were male, 302 female. The houses were mostly made from mudbrick and the walls were plastered with a white soil called "Çorak".

Geological samples taken from Corak earth and examined with x-ray diffraction method revealed mostly tremolite type asbestos fibres and some clay minerals.

Total air dust sampling was collected with Casella type air sampler and examined with both optical microscopy and electron microscope and the composition of the fibre analyzed with EDAX in conjunction with transmission electron microscopy. This study revealed 5.1 fibres in 1 ml ambient air. The length of most fibres were more than 10 microns.

Epidemiological Study:

A questionnaire was filled and a brief clinical examination was done on 130 people (56 males and 74 females) over 25 years old.

The average age was 33.3 years. Sixty-eight percent of the villagers examined were heavy smokers. More than 50% of the smokers complained of productive cough.

The positive findings on physical examination are shown in Table 20.

Table 20. Positive physical findings detected in 130 individuals from Sarikaya

Positive Findings	Number of Cases and Percentage
Rhonchi	21 (16.15)
Coarse crepitation	19 (14.61)
Fine crepitation	2 (1.53)
Digital clubbing	1 (0.76)

Chest x-ray was taken for 120 of the 130 persons for whom the questionnaire had been completed. Forty-five of the 120 chest x-rays were assessed as normal. The radiological findings are shown in Table 21.

Table 21. Radiological results of 120 persons over 25-year-old from Sarıkaya

Findings	Number of Cases and Percentage
Normal	45 (37.50)
Small opacities	29 (24.16)
Calcified Pleural Plaques	10 (8.33)
Pleural thickening	6 (5)
Parenchymal calcification	3 (2.50)
Tuberculosis	3 (2.50)
Rib fracture	1 (0.83)
Azygos lobe	1 (0.83)

Comment

Sarıkaya is another asbestos village in Central Anatolia. There was a high incidence of pleural disease due to environmental exposure to asbestos fibres. Malignant mesothelioma was diagnosed in a young patient from the village.

DISCUSSION ON 160 CASES OF MALIGNANT PLEURAL MESOTHELIOMA FROM ASBESTOS VILLAGES

A total of 160 cases of malignant pleural mesothelioma were collected from asbestos villages between 1975 and 1980.

Etiology: Environmental studies done on geological and airborne dust sampling together with some mineralogic analysis of lung tissues shows that asbestos is responsible for the diseases.

Villagers were mostly exposed to asbestos fibres in the environment. One of the most important methods of domestic exposure was from dusts originating from the walls of the houses that had been whitewashed with white stucco. Our airborne dust sampling clearly demonstrated this fact. Mineralogical analysis also showed that most of the white stucco, but not all, contained different types of asbestos together with clay minerals.

Studies also demonstrated that most of the roof earth contained asbestos and other minerals and many houses in the rural part of Anatolia used this grey-bluish colour soil for roofing and for insulation.

Furthermore, fibers originating from the asbestos deposits in the surrounding area was also another source.

Workers employed in the asbestos mills and mines and chrome mine in the Mihalıççık region were exposed to asbestos dust occupationally and could carry dust to their homes through their contaminated clothes, hair, shoes, equipment, etc.

Asbestos mixed baby earth which was commonly used in the rural region could also be accepted as an asbestos source.

In some villages, during preparation of grape molasses and wine, white soil was used in order to decrease acidity and increase the density of juice. Some of these soils were also contaminated with asbestos. One could also be exposed to asbestos fibres through the washing of laundry in water containing asbestos.

It was difficult to know which type of asbestos was responsible for the endemic diseases. Our studies in the villages showed that some of them had a high incidence of calcified pleural plaques and pleural thickening, but few cases of mesothelioma. On the other hand, some of the other villages had both benign and malignant pleural diseases

(12, 13). It is very well known that, pleural asbestosis can occur by inhalation of any type of asbestos and asbestiform minerals. We believe that heavy exposure to asbestos and asbestiform minerals of a certain size was responsible for the endemic pleural diseases in the rural part of Turkey.

Environmental studies have also shown that there are tremolite asbestos in the samples and its size is suitable for inducing malignant disease. Tremolite is an amphibole mineral found in several countries and is frequently found as a contaminant of other minerals that are being exploited commercially. In the Northern part of New York State, a finer tremolite occurs as a contaminant of talc deposits. From these mines there was evidence of pulmonary fibrosis, excess carcinoma of the lung and pleural and peritoneal mesothelioma (5, 6). Coarse tremolite fibres were found in certain agricultural areas of Czechoslovakia, Yugoslavia, Bulgaria and Greece (2, 8, 14). Some cases of mesothelioma were found among the people living in the vicinity of the asbestos mines in Cyprus.

Wagner (9), induced malignant mesothelioma in rats by using fine tremolite fibers obtained from South Korea. We have been informed that the mining operations have now been suspended because of suspected cancer among the workers.

The high incidence of malignant diseases in Mihallıççık, Sorgun and Southeastern part of Turkey may be related to the inhalation of fine tremolite fibres. A coarse flake-like tremolite fibre inhalation, may contribute to the development of benign pleural diseases and fibrosis.

Age and Sex: There were 102 males and 58 females. The ages of the males varied between 15-71, and average age was 42.8. The ages of the females varied between 7-69, and average age was 48.5.

It is well known that mesothelioma in asbestos workers is commonly diagnosed at ages 50-70 and the interval between the first exposure to asbestos and emergence of the tumour is usually 20 to 40 years (1, 3, 4). Our patients are younger than those of the others. This can easily be explained by the exposure to asbestos in their early life.

Mesothelioma was diagnosed in a 7-year-old offspring of a 35-year-old woman who died of mesothelioma. This case may point to familial susceptibility and perhaps transplacental transfer of asbestos fibres (10).

Mesothelioma has been reported in female asbestos workers. In our series the female patients have never worked in any asbestos industry. However, they are in the same environment as the men. They conduct their lives in their homes and the fields alongside their husbands. The fact that the female patients seen are less than the males may be due perhaps to the possibility that they do not come as often as the men.

Past and family history: Some of cases were treated as tuberculous pleural effusion for a long time. In 3 patients thoracotomy and decortication was done because of chronic pleural effusion and thickening. Histologic study had revealed only chronic fibrosing pleuritis, without malignancy. Malignant pleural mesothelioma developed on the same side in 2 cases and the other side in one patient after 5 - 7 years. In another case, pleural and peritoneal mesothelioma developed 4 years after decortication for benign fibrosing pleuritis.

A number of patients stated that there were similar cases in other family numbers. Familial mesothelioma has been reported previously (7, 11). In the patients at Garipler, beside inhaling the same air, familial susceptibility may be relevant to a certain extent.

In some cases, the clinical diagnosis of mesothelioma was supported by seeing pleural plaques in the chest x-rays of patients of close relatives.

Smoking habits: Information on smoking was available for 61 cases, and all were males. None of the female patients smoked. The study showed that cigarette smoking was not an important contributing factor to the development of mesothelioma. This has been stated in the previous reports.

Distribution of Cases in Turkey: The province of Yozgat occupies the first place with 20 cases, Konya is second with 14, Çankırı third with 13. Eight cases from Eskişehir and Tokat each, 7 cases from Elazığ, 6 cases from Sivas, 5 cases each from Çorum, Kütahya, Malatya, 4 cases each, Ankara, Diyarbakır and Niğde were detected. It is noteworthy that there was only one case each from İstanbul and İzmir, the biggest cities of Turkey.

All the cases were clustered in certain rural parts of Turkey, namely; Sorgun, Ereğli, Şabanözü, Mihallıççık districts. Most of the patients from the southeastern part of Turkey were evaluated in hospitals located there (12, 13). So, the number of patients from that area in our study will not be a true reflection of their actual number.

Clinical Manifestations: The mode of onset in all cases was insidious chest pain, and the interval before reaching hospital was six months. The pain started as a sensation of heaviness and coldness on one side of the chest and shoulder. Severe chest pain with shortness of breath was the classical picture in those patients in the terminal stage of the illness. Intractable chest pain, which also radiates to the upper part of the abdomen was usually seen in cases with tumoural chest wall involvement. Dyspnea was common in patients who had massive pleural effusion, mediastinal shift and cardiorespiratory failure. Orthopnea, cyanosis, restlesness, perspiration, clammy and cold skin, tachycardia and tachypnoea were always seen in the late stage.

The most common finding on physical examination of the chest was signs of pleural effusion. However, the presence of tumour on the chest wall and bronchial breathing were not uncommon. A sunken, immobile hemithorax, the so-called "Frozen chest" was a prominent finding in advanced cases.

Symptomatic hypoglycemia was observed in three cases with pleural mesothelioma.

Claude-Bernard-Horner's syndrome was detected in 8 patients in the late stage.

Hypertrophic pulmonary osteoarthropathy was not detected in our cases.

Radiological findings: The most common radiological findings were pleural effusion with or without pleural thickening. In some cases, peripheral pleuro-pulmonary nodular opacities, hydro-pneumothorax, tumoural mass on the chest wall and rib erosion were also seen. Calcified pleural plaques on parietal pleura, diaphragm, pericardium and diffuse lung fibrosis were also encountered as associated findings.

In some cases mediastinum was not shifted because of fibrosis.

We had the opportunity of collecting 131 patients' chest x-rays and re-evaluated them. The findings are shown in Table 22.

Table 22. Radiological findings in 131 cases of pleural mesothelioma from asbestos villages

Findings	Number and percentage	
Pleural effusion	74	56.48
Pleural thickening with or without Pl. effusion	24	18.32
Peripheral pleuro-pulmonary nodules	14	10.68
Calcified Pl. Plaques with Pl.ef. and thickening	12	9.16
Hydro-pneumothorax	4	3.05
Chest wall tumour with pl. disease	2	1.52
Rib erosion with pleural dis.	1	0.76

Laboratory investigations: The minimal erythrocyte sedimentation rate was 4 mm/hr and the maximal was 115 mm/hr. The pleural fluid showed polymorphism, that is, exudate, sero-hemorrhagic and hemorrhagic. The protein content was a minimum of 1 gm percent and maximum 6.2 gm percent. The amount of glucose in the pleural fluid was 150-130 mg percent. Values below 15 mg percent of pleural fluid were detected in 3 cases. Hypoglycaemic attacts which immediately corrected on the administration of IV glucose were seen in 2 cases. A third developed shock following pleural tap and died. Glucose level in the pleural fluid of this patient was 0. Pleural fluid LDH level was measured in 1/3 of patients and values above 200 IU were obtained in all of these patients.

Diagnostic methods: The method of diagnosis in the 153 patients are shown in Table 23.

Table 23. Method of diagnosis in 153 cases of mesothelioma from asbestos villages

Method	Number and Percentage	
Thoracotomy	75	49.01
Pleural needle biopsy	36	23.52
Thoracoscopy	19	12.41
Clinico-radiological	10	6.53
Biopsy of the tumour on chest wall	7	4.57
Autopsy	6	3.92
TOTAL	153	100%

Tumoral implantation on the site of biopsy or thoracotomy was observed on 5 patients.

In a large majority of patients thoracotomy revealed inoperable disease and the procedure was only diagnostic. Decortication was done in 11, pleuro-pneumonectomy on 7 and lobectomy and decortication in one patient. Of the patients we were able to follow-up, only one who had decortication is still alive.

Management: Chemotherapy either with a single agent (Doxorubicin) or a combined regimen was given in 18 of our patients. The results were not encouraging. Palliative radiotherapy done in 10 patients for tumoral infiltration in the chest wall, only resulted in temporary reduction of tumour size. Pleurodesis was performed on 8 patients with massive pleural effusion and some temporary benefit was obtained. Intrapleural BCG applied in two cases caused long standing febrile reaction without any beneficial effect.

Most of the patients died within 12-18 months of coming to the department. The cause of death was mainly cardiorespiratory failure.

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CLINICAL EVALUATION OF 13 CASES OF ASBESTOS PLEURAL EFFUSION

We collected 13 cases of asbestos pleural effusion from the asbestos villages.

The diagnosis was based on the criteria mentioned below:

1. Definite elimination of infectious, malignant and collagenous diseases which cause pleural effusion as well as the diseases which lead to accumulation of transudative pleural fluid.
2. The patient should come from asbestotic village or must be occupationally exposed to asbestos.
3. The course of the disease must be chronic and of benign character. The patient must appear healthy looking and have no obvious symptoms, except vague chest pain. He should not have fever, loss of appetite or weight loss.
4. Clinical and radiological examination should reveal small or mild pleural effusion. The patient must respond well to fluid aspiration and the fluid should not re-accumulate over a short period.
5. Presence of other lesions, such as calcified or hyalinized pleural plaques with pleural effusion.
6. Histologic examination of tissues taken by biopsy needles, thoracoscopy or thoracotomy must reveal only fibrosis without granulomatous infiltration and malignancy.
7. Thoracoscopic or thoracotomic view must be compatible with chronic fibrosing pleuritis.
8. Cytological and bacteriological studies on the fluid must be negative for malignancies and infection.

Table 24 gives some information obtained from the charts of 13 cases of asbestos pleural effusion.

In patients 2, 5, 11, and 13, mineralogical examination done on the pleura and lung tissues showed asbestos fibres. Histological examination of the lung tissue in case 13 revealed tuberculous granulomatous infiltration in addition to chronic fibrosing pleuritis and lung fibrosis.

Table 24: Information of 13 Cases of Asbestos Pleural Effusion Collected from Asbestos Villages

Patient Age / Sex	Origin	Diagnostic Method	Management	Follow-up Period (years)
1. S.K. 25 - Male	Sunurlu - Kurşunlu/ Çankırı	Thoroscopy	Fluid Asp.	6
2. M.G. 44 - Male	Hacıhamzalı Tarsus - Mersin	Thoracotomy	Decortication	13
3. R.K. 26 - Female	Çermik - Diyarbakır	- do -	- do -	8
4. H.K. 65 - Male	Erbaa - Tokat	- do -	- do -	8
5. M.D. 48 - Male	Söğüt - Burdur	- do -	- do -	6
6. S.A. 67 - Male	Gümüş - Merzifon Amasya	- do -	- do -	9
7. M.O. 45 - Male	Adana	- do -	Fluid Asp.	8
8. H.O. 60 - Male	Güney - Yeşilova Burdur	Clinico-radiological	- do -	5
9. A.K. 60 - Male	Gökçeyazı - Ereğli - Konya	- do -	- do -	5
10. M.K. 60 - Male	Kayı - Mihallıççık - Eskişehir	- do -	- do -	8
11. V.T. 43 - Male	Yeşilova - Burdur	Thoracotomy	Decortication	4
12. O.K. 50 - Male	Hekimhan - Malatya	Clinico-radiological	Fluid Asp.	4
13. R.B. 52 - Male	Southeastern A.	Thoracotomy	Decortication	4

In the patients diagnosed by clinical and radiological findings, there were classical asbestos related calcified pleural plaques in their chest x-rays and furthermore they were from asbestos villages where there was a high prevalance of endemic pleural diseases.

MALIGNANT DISEASES AND PLEURAL ASBESTOSIS

During the studies on asbestos related diseases, we encountered some interesting cases who demonstrate the relation between benign asbestos related chest disease and malignant diseases.

Case 1: A 25-year-old male originally from a village in Sungurlu district of Çorum province. He had thoracotomy and decortication because of chronic pleural effusion, 4 years previously. Histological examination of resected tissues showed chronic fibrous pleuritis.

His main complaint was severe chest pain on the operated side. Second diagnostic thoracotomy revealed inoperable malignant pleural mesothelioma on the same side.

Case 2: A 39-year-old lawyer who had been born and raised in Hatay. He had been followed-up for 4 years because of pleural effusion on the left side. Multiple pleural needle biopsies revealed chronic fibrous pleuritis. He was given therapy for tuberculosis. Although a mild response was obtained he was never normal. He was refered to our department and physical and radiological examination revealed left sided pleural effusion. During diagnostic thoracotomy multiple grape-shaped nodular lesions were seen on both visceral and parietal pleura and on the diaphragm and both pleura appeared thickened. Some hyalinized pleural plaques were also seen on the left hemidiaphragm. Extensive decortication was done and histology revealed malignant pleural mesothelioma. Mineralogical studies on pleural and lung tissues done by Patrick Sebastien, Laboratoire de Recherches sur les Affections Respiratoires et L.Environnement, Paris, France, reported that 1 gram dried lung tissue showed 7×10^2 asbestos bodies by optic microscopy and there was 3×10^6 actinolite type asbestos fibers by electron microscope. No fibers were seen in the pleural tissues.

The patient was followed-up for 3 years and during this period, although there was no recurrence of fluid accumulation, he continued to complain of chest pain.

Case 3: A 50-year-old male patient from the Yaycılar village of Sorgun-Yozgat, His Physical examination revealed pleural effusion and calcified pleural plaques on the right side. Thoracentesis yielded a hemorrhagic pleural effusion but pleural biopsy was non-diagnostic. Although our clinical impression was malignant pleural mesothelioma, bronchoscopy revealed small cell bronchial carcinoma.

Case 4: A 73-year-old female patient, born in one of the asbestos villages of Diyarbakır province. Her main complaint was severe chest pain and physical examination revealed diminished air entry with bronchial breathing. Chest x-ray showed extensive calcified pleural calcification together with a mass on the right upper zone. There was also rib erosion close to the tumour. Bronchoscopic biopsy showed small cell bronchial carcinoma. She had never smoked throughout her life. Fig. 9 shows her chest x-ray.

Case 5: A 53-year-old female patient from Yıldızeli, Sivas. She was admitted into hospital because of hemoptysis. Physical examination revealed diminished air entry and fixed rhonchi on the left side. Chest x-ray (Fig. 10), showed left hilar mass and multiple calcified pleural plaques. Bronchoscopy revealed narrowing of the left main bronchus. Blind biopsy from the narrowed area and bronchial lavage were non -

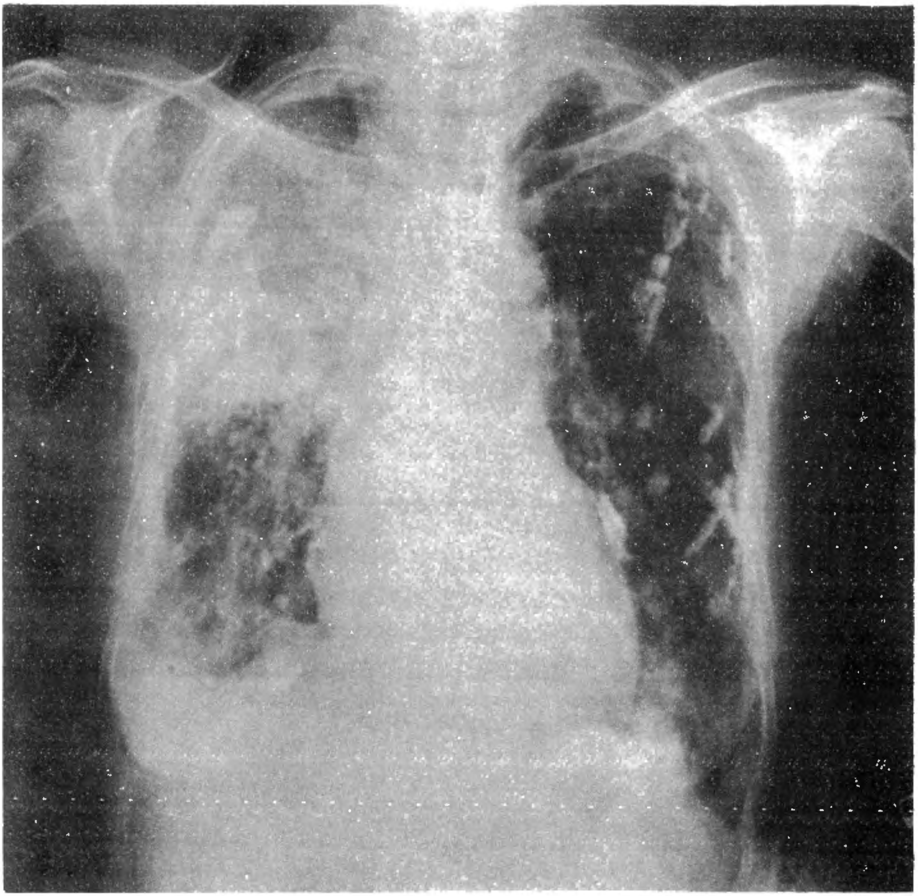

Figure 9. Carcinoma of the lung with extensive typical bilateral pleural, pericardial and diaphragmatic calcification. A non-smoker middle aged female patient from an asbestos village in the southeastern part of Turkey.

diagnostic. Thoracotomy however revealed an tumour mass on the left hilum. Biopsies from the mass showed large cell bronchial carcinoma.

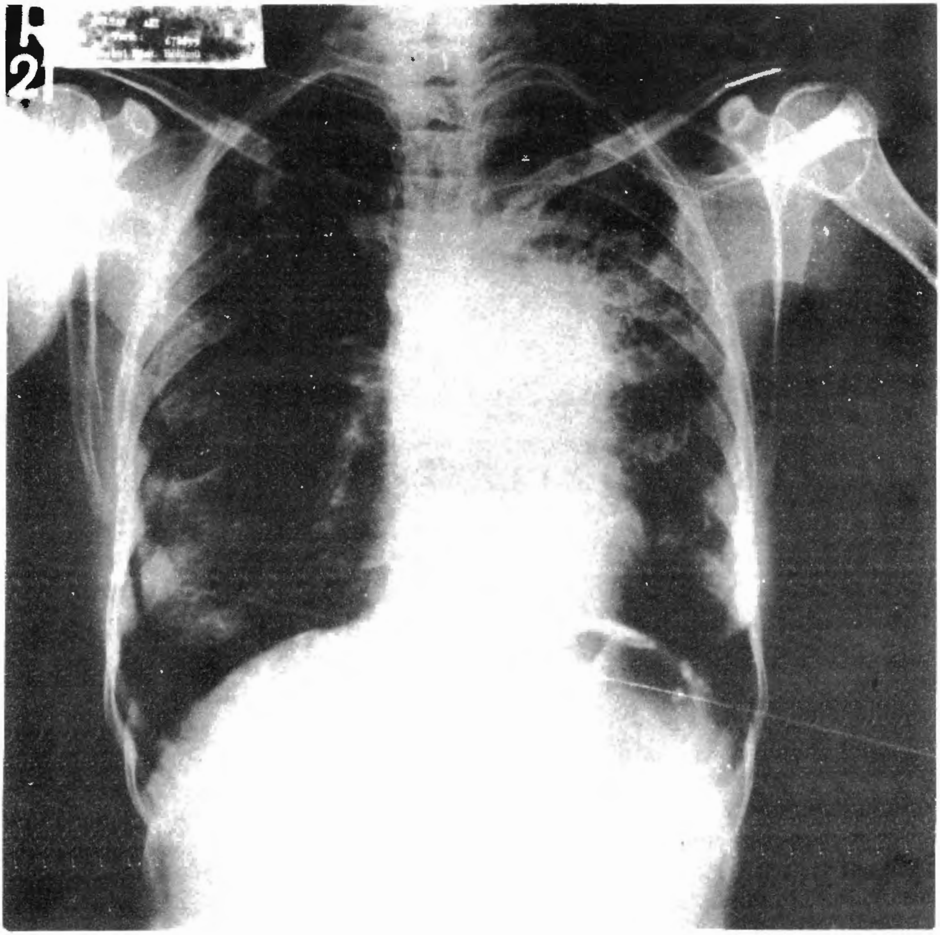

Figure 10. Carcinoma of the lung with bilateral pleural and diaphragmatic calcification. A non-smoker middle aged female patient from an asbestos village in central Anatolia.

DISCUSSION

The first and second cases had chronic fibrosing pleuritis histologically followed by the development of malignant mesothelioma 4 years later. Although an increased risk of mesothelioma in diffuse pleural fibrosis is mentioned, there is no objective data to support this. Benign asbestos-induced pleural diseases have not been accepted as precursors of malignant diseases. However, if the host is carrying carcinogenic and fibrogenic material, there will be an increased risk of developing fibrosis and malignanciy.

The survival time of mesothelioma after diagnosis is dependent on the stage of the disease and the histologic type. The epithelial type of mesothelioma has a better prognosis than the mixed and sarcomatous ones. For all mesotheliomas, the median survival from the appearance of first symptoms is about 10 months (4). The median survival times for epithelial, mixed and sarcomatous types are 10,10 and 5 months, respectively. Long-term survivors, i.e., 3 years or more occur almost exclusively in the epithelial group (4). There are reported cases who have been followed-up for 7 years (1, 5, 6).

Gaensler and associates (3) suggested 4 criteria for the diagnosis of benign asbestos pleural effusion. One of these criteria is "No malignant tumor detected within 3 years after the effusion". They advice early exploratory thoracotomy and decortication for definite diagnosis, to correct compromised lung function and to prevent further recurrences. Fifteen cases of benign asbestos pleural effusions were operated on and follow-up ranged from 3 to 14 years. Six of these patients were well when last seen; 2 patients died of mesothelioma; 1 of a lesion of the pleura 9 years after operation and 1 of an abdominal tumour after 12 years, 1 died of bronchogenic carcinoma 3 years after biopsy and 2 died of asbestosis 1 and 2 years later.

The third case, again demonstrates the relation between bronchial malignancy and calcified plaques.

The fourth and fifth cases reveal bronchial carcinomas in non-smoking women. Fıratlı and co-workers (2) pointed out the high incidence of pulmonary malignant diseases in female patients. In the rural part of Turkey, females rarely smoke. The presence of malignant disease with calcified pleural plaques again demonstrate the association between bronchial carcinoma and benign pleural disease due to asbestos.

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SUGGESTED PREVENTIVE MEASURES FOR ASBESTOS VILLAGES

Our surveys and research studies have shown that asbestos - related diseases are a major threat to health in many villages in Central Anatolia. These diseases which are due more to environmental than occupational exposure to asbestos can be minimized considerably if proper preventive measures are instituted.

Health education will play a major role here. The villagers should be educated on the hazards of using asbestos contaminated white soil as plastering material and baby powder. They should avoid using grey ground (Çeren or Çorak) as insulation material in the roofs of their houses. These and other information may be disseminated through radio broadcasts, newspapers, television programs or at Friday prayers.

Mining of white soil should be banned and the open white stucco deposits should be covered.

Walls plastered with white stucco should be repainted with whitewash or plastic paint. These materials should be made easily available to the villagers.

Undergraduate and postgraduate residency training programme in medicine should lay emphasis on asbestos related diseases. General practitioners working in health centers of the villages in endemic areas should have their knowledge in these diseases regularly updated.

All microfilms taken by the Tuberculosis Control Units during screening for tuberculosis should be re-evaluated by physicians who have experience in asbestos-related diseases.

In endemic areas, radiologic and clinical screening should be carried out at least once a year, for early diagnosis of disease.

These preventive measures should also be instituted in dewly discovered asbestos villages.

PART II

ZEOLITES

A. MINES, DEPOSITS, PRODUCTION AND USES

B. FIBROUS ZEOLITE (ERIONITE) RELATED DISEASES IN TURKEY

- INTRODUCTION
- KARAİN - ÜRGÜP/NEVŞEHİR RESEARCH
- TUZKÖY - GÜLŞEHİR/NEVŞEHİR RESEARCH
- SARIHIDIR - ÜRGÜP/NEVŞEHİR RESEARCH
- CLINICAL EVALUATION OF 94 CASES OF MALIGNANT PLEURAL MESOTHELIOMA FROM ERIONITE VILLAGES
- DISCUSSION
- CONCLUSION ON ERIONITE - RELATED DISEASES
- SUGGESTED PREVENTIVE MEASURES FOR ZEOLITE VILLAGES

ZEOLITES

Mines, Deposits, Production and Uses

Zeolite minerals is a generic term for various crystalline aluminosilicates of alkali and alkaline earth cations having a three-dimensional silicate structure. They are characterized by the ability to lose or gain water molecules and to exchange cations, without major change of the crystal structure. Natural and synthetic zeolites may occur in granular or fibrous forms.

Zeolites were first discovered as a new group of minerals by Cronsted, a Swedish mineralogist, with the discovery of Stilbite in 1756. The word zeolite was coined from two Greek words meaning To Boil = Zein and A Stone = Lithos, boiling stone because of the loss of water when heated in the mineralogist's blowpipe.

It is believed that zeolitic tuff was first used during the Roman empire, to build houses and to construct roads and sewage channels (11, 13). Most of the milestones were from zeolite stones, a large quantity of which were collected from the Pozzuoli region of Italy. Volcanic tuffs collected from the underground quarries of Napoli, were easily sculptured and shaped and used for the front part of government buildings.

After the second half of the 20th century, zeolites became industrial minerals. Over 1000 deposits of zeolite minerals have been reported from sedimentary rocks of volcanic origin in more than 40 countries. In U.S.A., Bulgaria, Hungary, Japan, South Africa, Mexico., Cuba, South Korea, Czechoslovakia, Romania, U.S.S.R., Yugoslavia, The People's Republic of China, Italy, New Zealand, West Germany and Turkey all have zeolite mines.

Most of the mines are designed to mine clinoptilolite and/or mordenite, although chabazite and phillipsite are also mined. World production of natural zeolites has been estimated at 300,000 tons per annum (12). Clifton (6-8) estimated that the annual zeolite production for the years 1982-1984 was 2500 - 5000 tons.

There are more than 30 species of natural zeolites and they tend to occur in mixed deposits contaminated with other volcanic minerals. Some of the natural zeolites are shown below (10, 14).

Natural Zeolites:	
Analcime	Heulandite
Chabazide	Laumontite
Clinoptilolite	Mordenite
Epistilbite	Natrolite
Erionite	Phillipsite
Faujasite	Scolecite
Ferrierite	Stilbite
Gismondine	Thomsonite
Gonnardit	Wairakite
Harmotome	Yugowaralite

Analcime, chabazite, clinoptilolite, erionite, ferrierite, heulandite, laumontite, modenite and phillipsite make up the major part of zeolite rocks.

Zeolites occur in rocks deposited in diverse geological environments and age and have been classified into several types (11, 12):

1. Deposits formed from volcanic materials in "closed" saline-lake systems.
2. Deposits formed in "Open" fresh water-lake or groundwater systems.
3. Deposits in marine environments.
4. Deposits formed by low-grade, burial metamorphism.
5 Deposits formed by hydrothermal or hot-spring activity.
6. Deposits formed from volcanic materials in alkaline soils.
7. Deposits formed without direct evidence of volcanic precursors.

Most zeolites in sedimentary rocks are formed from volcanic ash or other pyroclastic material by reaction of the amorphous aluminosilicate glass with pervading pore waters. Others originate by the alteration of pre-existing feldspars, feldspathoids, biogenic silica or poorly crystalline clay minerals. Although the exact machanism of formation is still under investigation, zeolites in sedimentary rocks are probably formed by means of dissolution-reprecipitation reaction with or without an intermediate gel stage. The factor controlling whether a zeolite or a clay mineral will form from a given starting material is also only poorly understood, although temperature, pressure, reaction time, and the activities of dissolved species such as pH, silica, alumina, and alkali and alkaline earth cations seem to be important.

Erionite: Most of the zeolite species are non-fibrous, but at least two of the natural zeolites, mordenite and erionite which have potential value have a fibrous habit.

Erionite is a naturally occuring fibrous zeolite mineral having the approximate chemical formula $(Na_2, K_2, Ca, Mg)_{4.5} (Al_9, Si_{27}, O_{72}) \cdot 27H_2O$.

Erionite was first decribed and named by Eakle in 1898. The name is derived from the Greek word for wool. Erionite may be in the short-fibered or long-fibered form.

In the U.S.A., erionite and other zeolites are found in deposits in Oregon, South Dakota, Nevada and Arizona (14). There are also some deposits in Japan, Yugoslavia, Kenya, Tanzania, New Zealand, Mexico and Turkey.

The percentage of erionite in the zeolitic tuffs is changeable. Zeolite layers up to 210 cm thick containing 10-100% erionite have been described in Nevada (16). Zeolite deposits in Japan also have large amounts of erionite. According to Mumpton (11), there are six mineable deposits of erionite in U.S.A., but only two have been mined. Companies no longer mine for pure erionite deposits and it is believed that at the present time, erionite is not mined for commercial use anywehere in the world. The chabazite/erionite deposit in Bowie, Arizona was mined extensively by one U.S. Company in the early 1970s at levels exceeding 80,000 tons annually (9).

Erionite-rich rock has been quarried in the Western U.S.A. for house-building, but its use for this purpose is not due to its mineral content (11, 13).

Synthetic zeolites: These have been produced commercially in the U.S.A. They are used primarily as catalysts, selective sorbents, and desiccants in petrochemical industry. Linde A, Linde X and Linde Y are some synthetic zeolites. All synthetic zeolites are non-fibrous.

Zeolites are characterized by an open lattice structure and are thus useful for filtration, catalysis and absorption in the chemical industry and agriculture.

Industrial and commercial uses of zeolites (11, 14):

1. Pollution-control: Ion-exchange and absorption properties of zeolites
   a. Radioactive-waste disposal
   b. Sewage-effluent treatment
   c. Agricultural-waste water treatment
   d. Stack-gas cleanup
   e. Oil-spill cleanup
2. Oxygen production: Nitrogen gas is selectively absorbed from air by several zeolite materials yielding products containing up to 95% oxygen. The best natural zeolite for oxygen production is mordenite, but certain clinoptilolites and chabazites also appear to be useful.
3. Energy-conservation significance
   a. Coal gasification: Zeolites have the potential in the removal of SO2 from stackgas emissions, thereby allowing high-sulphur coals to be used in the production of electricity. Zeolites absorb nitrogen selectively from air and produce oxygen rich products.
   b. Natural gas purification.
   C. Solar energy use
   d. Petroleum production

4. Agricultural uses
   a. Fertilizer uses: Based on their high ion-exchange capacity and water retention, they have been used extensively as soil conditioners, to control the moisture content of soil and malodour of animal manure and to neutralize low pH of soils.
   b. Herbicide and pesticide carriers: Natural zeolites have been used as effective carriers of herbicides and pesticides.
   c. Animal nutrition: As a dietary supplement in animal husbandry.
   d. Animal-waste treatment: Natural zeolites have potential application in several areas of manure treatment, including reducing the malodour of the excrement, controlling the moisture content for ease of handling and purifying methane gas produced by the anaerobic digestion of such materials.
5. Importance in mining and metarlurgy
   a. Exploration
   b. Hydrometallurgical uses
6. Miscellaneous applications
   a. Paper products
   b. Construction
   c. Medical applications: Clinoptilolite as a polishing agent in fluoride-containing toothpaste; for separation of ammoniacal nitrogen from hemodialysis liquids.

Burd and Maziuk (5) reported that erionite was used as a catalyst in one American Company's hydrocarbon cracking process.

Erionite has been studied for use as an ammendment to increase soil fertility (4) and for odour control in livestock production (15). It is doubtful that materials marketed as erionite are used for either purpose at the present time.

Zeolite Deposits in Turkey

Zeolite deposits were first reported by Ataman and Beseme in the regions of Bahçecik-Gölpazarı-Göynük at 1972 (1). Later on analcime and clinoptilolite deposits were found on the west part of Ankara province (2).

Reported zeolite deposits in Turkey are:

1. Bahceçik - Gölpazarı - Göynük region: Analcime species.
2. Polatlı-Mülk-Oğlakcı-Ayas; Analcime species
3. Bigadic/Balikesir: Osmancı, Kısakayatepe and Kadıköy: Clinoptilolite species
4. Saphane/Kütahya: Clinoptilolite. Hisarcık/Gediz, Clinoptilolite and analcine: Yukarı Yoncaağaç - Emet, clinopitilolite species.
5. West Anatolia: Gördes, Urla, Kırkağaç, and Yağmurlu: Clinoptilolite species
6. Cappadocia region of Central Anatolia

After reporting endemic mesothelioma in Cappadocia region Ataman (3) surveyed the region and found clinoptilolite, chabazite, mordenite and erionite types of zeolites, mainly in Tuzkoy, Karain and Sarihidir villages.

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ERIONITE RELATED DISEASES IN TURKEY

INTRODUCTION

We were informed by the head of Karain village that there were many cases of cancer in the village and we subsequently invited him to our department for further discussion of the subject. After a couple of weeks, İlyas Yiğit, the head of the village, Mustafa Özkan, the Karain Health Center Officer and a 40-year-old patient B.K. arrived in Ankara.

Mustafa Özkan provided us with good documented case histories of patients who had died or were still ill in the village. These indicated that there was as yet an unidentified but serious disease in the village.

We admitted the patient and clinical and radiological study suggested that he could have malignant pleural mesothelioma. A needle biopsy of the pleura confirmed this diagnosis.

According to the clinical notes provided, most of the patients were hospitalized in the local chest hospital and were treated as tuberculosis, but did not respond. Few of them were admitted in the Chest Diseases Unit of Ankara University School of Medicine and Keçiören Atatürk Sanatorium. There was only one patient who was admitted into the ENT Department of Hacettepe University Hospitals.

We collected all the case files of the patients who were hospitalized in the Chest Hospital of Kayseri, Chest Diseases Clinic of Ankara Medical School and Keciören Atatürk Sanatorium. After reviewing the files, we formed the impression that the clinical and radiological picture strongly suggested malignant pleural mesothelioma. Some of the patients who were admitted in Ankara Hospital also had tissue diagnosis.

The case file of the female patient who had been admitted into the ENT Department of Hacettepe University Hospitals was interesting. She was about 35 years old, and was diagnosed as esophageal carcinoma by biopsy. In her family history, she mentioned that, her father, uncle and brother died from carcinoma.

After interview with the head of the village and health center attendant, and the diagnosis of the first patient as malignant pleural mesothelioma, we decided to do a survey in Karain.

Our initial impression was that there were many malignant mesotheliomas in Karain village and we expected to find asbestos there.

We arranged a preliminary meeting with A. Göktepeli, a geologist from the Institute of Mineralogical Research and Exploitation (MTA). He informed us that the geological maps of Cappadocia region, did not show any deposits of asbestos.

A team, consisting of physicians, a geologist and a mineralogist first visited Karain village in the summer of 1975.

Before we started the study, we discussed the problem with the residents of Karain. They were all very enthusiastic about our visit and met us in the caffee house in the center of the village. The middle aged and old peasants made some very interesting and puzzling comments. Here are some of them:

"The name of this village comes from "Karın ağrısı" which means abdominal pain. This term has gradually changed to Karain." However, some of the villagers held a contrary view. They believed that the name Karain was derived from, Kara and In. "Kara" means black, "In" means cave. They think that, black dwelling caves made by man inside fairy chimneys just behind the village gives the name of village.

"The villagers of Karain fall ill with pain in the chest and belly, the shoulder drops and they die."

"I can't remember my father, and he does not remember his father".

"Women who are originally from other villages live longer than the females from Karain."

"People who are born and raised in Karain and who move to other villages or cities for various reasons, such as marriage or to look for jobs also suffer from the same diseases as those who remain in Karain. They can't get away from Karain's diseases. If you are born in Karain and live for a short time here, it is enough to get the disease."

"Our religious leader who is responsible for the mosque is more active than those of the other villages. If you compare the size of the cemetery of Karain with those of the other villages, you can easily see the difference."

"You can easily see that the number of old people in Karain is less than those of other villages."

"If we ask girls from other villages for marriage, they are usually reluctant because of the possibility of early widowhood. It is the same with the men, they don't want to have a bride from Karain either."

"The disease is characterized by fluid accumulation in the chest and abdomen."

"The disease is a killer. It is insiduous in onset, progresses slowly and all the patients have severe pain."

"Most of the patients have been treated as tuberculosis without success or benefit. We believe that the disease is not tuberculosis".

"Some of our patients have tumoral growth on the chest wall or in the abdomen. They call it "TOPAK". Topak means a solid mass."

"Those patients who accept operation either for the chest or abdomen, suffer more and die early. We believe that operation is without benefit and is hazardous. It is an open and close operation."

"The disease is familial and is worse in some families. If you visit the cemetery and look at the head stones of cement you will easily see that Can, Gürbüz, Süllü, Kara, Şencan, Genç and Pehlivan families have suffered most."

"The disease strikes mostly middle aged males and females. It is rarely seen in young people."

Chronic disease associated with chest and abdominal pain and fluid accumulation in the chest and abdomen, that is not helped by medical or surgical therapy is most likely malignant pleural or peritoneal mesothelioma.

We examined all the patients and took their chest x-rays with a portable machine. We also took biopsies from the pleura from those patients who had pleural effusion. We were rather surprised at the results. We had been to many villages with asbestos deposits, but had never seen such a large number of patients with possible asbestos-related disease.

The impression of the geologists and mineralogist was, "There are no asbestos deposits here. There are only volcanic tuffs".

Mineralogical analysis did not show asbestos fibres. This was quite surprising since we expected to find asbestos. Some samples were sent to the Earth Sciences Faculty of Hacettepe University and Mineralogy Department of Middle East University Technology (ODTU) for further evaluation. The results were the same, "No asbestos at all".

Pathological studies of the biopsy specimen taken in Karain, revealed malignant tumor.

We realized that, the picture was quite unique and needed some experts who have a good knowledge of clinical, radiological, pathological, epidemiological and mineralogical aspects of asbestos related diseases.

We wrote to the Director of MRC, Pneumoconiosis Unit, Llandough Hospital, S. Glamorgan, Penarth about the diseases in Karain. They were also interested and kindly invited us for discussion of our data.

The first meeting in Penarth was held in late 1977 in the pneumoconiosis unit. At that meeting, there were clinicians, a radiologist, pathologists, dust physicist, geologist and mineralogist. It was chaired by P.C. Elmes, Director of the unit. He also invited Dr.J.E. Milne from the International Agency Research of Cancer (IARC), Lyon, France.

During the session, the clinical picture was discussed. All chest x-rays and the tissue samples from some of our patients were re-examined. The dust and rock samples that I had sent earlier were analyzed.

During the meeting, they asked many questions relating to occupational, and environmental asbestos exposure, the living conditions of patients, radiation, any diseases in local animals, the possibility of autopsies, etc.

They confirmed that the dust and rock samples did not contain asbestos.

The subject was found fascinating and it was felt that there is an urgent need for further research and the help of IARC. Dr. Milne, promised to convey the massage to the director of the Agency.

P.C. Elmes received a positive response from the IARC and planned a visit to Turkey. He himself together with I.Thornton from the London Royal School of Mines, Department of Geology, and J.E.Milne arrived in Ankara on October 11, 1977. During their short stay, we visited Cappadocia area, mainly Karain and Tuzkoy and their neighboring villages and Hacihasan Village of Ilgaz/Cankırı which is an asbestos village. Elmes saw the patients, and their x-rays, and reviewed the 70 mm-microfilms of the inhabitants of Karain and neighbouring villages which were taken during the screening for tuberculosis by the Department of Tuberculous Control, Ministry of Health and Social Affairs. Thornton took many soil and rock samples from the roads, the quarries and the fields.

The results of this visit were discussed in the pneumoconiosis unit, Penarth on December 8, 1977. After the discussion, we all agreed that the disease was malignant pleural mesothelioma, the incidence was very high and there was no exposure to asbestos and that another fibrous mineral might be the cause. The result was submitted to IARC for them to arrange a research project in this area.

IARC accepted to carry out urgent research studies on this subject and this was started in 1978. It was conducted by the Department of Chest Diseases Hacettepe Medical School, MRC. Pneumoconiosis Unit and Department of Mineral Exploitation of the University College of Cardiff and Unit of epidemiology and biostatistics of IARC.

The research study lasted more than 4 years. F.D. Pooley from the University College of Cardiff was the first to demonstrate Fibrous Zeolite (Erionite) to be responsible for the cause of malignant pleural mesothelioma in Cappadocia.

KARAİN - ÜRGÜP/NEVŞEHİR RESEARCH

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ENVIRONMENTAL STUDY

General Information:

The village of Karain lies 25 kms. east of Nevşehir, in Cappadocia well known to tourists because of the picturesque rock dwellings called "Fairy Chimneys". It is located at the northern tip of a valley, lying 4-7 kms. to the south. Figure 11 shows the localizations of the zeolite villages, namely, Karain, Tuzköy and Sarıhıdır and their neighboring villages.

The history of the villages goes back a long time, to Selçuk Turk. We were informed that, Anatolian Christians lived on this volcanic area between Kayseri and Tuzgölü from 4-14 century. These people carved the tuff columns conical shaped fairy chimneys, made shelters, churches and work places. As protection against attacks by the Romans of that period, they lived inside the caves. In the 11th century, Selçuk Turks came to the neighbourhood and, for many years, the Christians and Turks lived peacefully side by side. After the foundation of the Turkish Republic, the Anatolian Greeks in the region migrated to Greece and the Turks from there to Cappadocia. Its present inhabitants are Turkish people of Selcuk descent and from Macedonia.

Although the population of the village was over 800 in 1974, with the adoption of birth control methods, the high incidence of premature deaths from malignant disease and migration to places both within and outside the country, it had fallen to

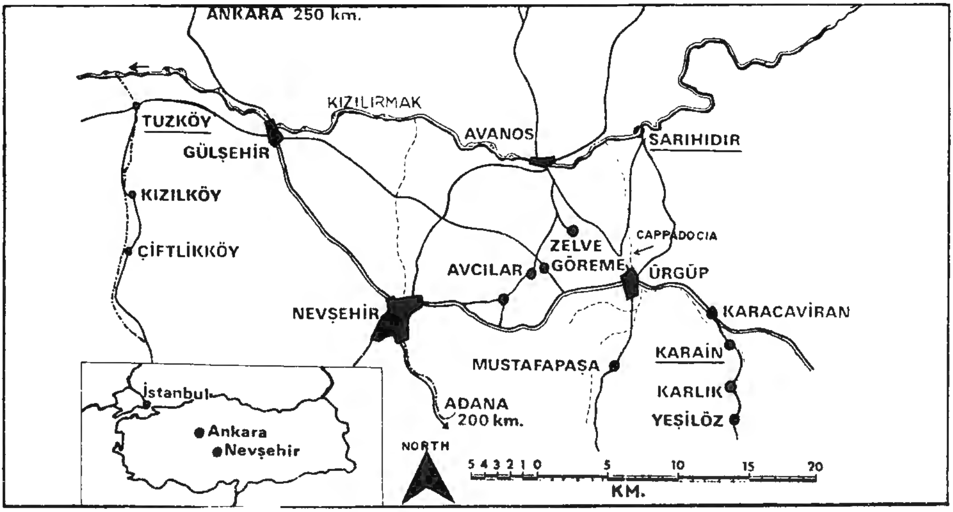

Figure 11. Map of the Cappadocia region showing the Zeolite villages of Karain, Tuzköy and Sarıhıdır.

554 in 1980. The country in which most people from Karain are found in Sweden.

The inhabitants of Karain are mainly farmers. In the past they grow and sell potatoes, onions and onion seeds. Some have apricot, apple trees and grape vines and a large section of the villagers also keep cattle.

The climate is hot and dry in summer and cold with snow in winter. Although the village's water supplies are plentiful, they have extensive fields with dry and poor soil. Irrigation is necessary and it continues 24 hours a day. Since there are almost 50 widows in the village, the watering is assigned to the women during the day and the men at night. In the intervals, they lie down and take a nap on the soft, dry tuff-containing soil.

Both natural and artificial fertilizers are used. During the planting season, they sieve the tuff containing soil that is mixed with fertilizer and this is then put on to newly planted onion seeds. They inhale a lot of dust at this time.

Every family in the village has a house, a barn and a courtyard and also annex for use as food stores, granary and depot. The structure, floor and walls of all the old houses are constructed from volcanic rock. The walls of some sections and the floors of courtyards are made by easily scraped volcanic tuff which becomes dusty and breaks easily. Since it is very soft and fragile, the villagers call it "Su Kayası".

There are many rock dwellings and fairy chimneys just behind the village. Most of the old houses to the rear of the villages have been abandoned, because of the danger of rock fall and collapse.

The building stones in Karain come from 5 sources. These are:

Örencelik Rock or Karlık Stone: From the quarries between Karlık and Karain. It has been used for more than 50 years. More than half of the houses of Karain are made from this stone. It is also used by Karlık people.

Akkuşak Stone: Collected from the hills to the northwest of the village. It is massive and well stratified. There are no more than 10 houses made from this stone. The village library is also built with this stone.

Geçit Stone: The source is located on the right side of Ürgüp-Kayseri highway, in the area near Incesu. It is hard, dark-reddish brown and its use began after 1960. Geçit stone is now used for new houses.

Nevşehir (Ürgüp) Stone: It is a multicolored soft stone obtained from either Nevşehir or Ürgüp. It is used mostly on the front walls of new buildings. This stone is used only in new houses built by guest workers.

Village Stones: These are hard, basalt type round stones found in the fields and are brought down by floods.

In the past, villagers whitwashed their walls with white stucco which was obtained from an area 1.5 kms. from Karacaviran village on the right side of the Ürgüp-Kayseri highway. The white stucco from the same source is also used by other neighbouring villages.

Recently, the residents of Karain, like those of the other villages, dig out the tuff around the village and make underground depots which they use for the cold storage of their products.

Water is obtained from: (a) the river; (b) the springs; (c) wells in the fields; and (d) a spring in the hills behind the villages which is called "Pınarıngözü" and piped to a communal tap in the village. The villagers are mainly dependent on the piped water, which has been available for over 100 years, for drinking, washing and cooking. Recently, artesian wells have been dug and they provide more piped water. None of the systems contain asbestos pipes.

Although the road which cross the village has been asphalted a number of times, the edges are covered with earth. In rainly weather, the muddy water that comes down to the road from the fairy chimneys and conical hills, breaks it up and a lot of dust results when it dries up. It is common for a thick cloud of dust to arise in the wake of the numerous vehicles that ply the village road and behind animal flocks and heards.

There is no difference between Karainers and other neighbouring villagers with regard to their customs, living and working conditions and other activities.

Geological and Mineralogical Study: Karain, Karlık, Tuzköy and Sarıhıdır

The Central Anatolian region between Kayseri and Tuzgöl was covered with plateaus of volcanic tuff engulfed from Mount Erciyas. The villages in which mesothelioma was observed, as well as much of Cappadocia, are built upon and into, tuff. Volcanic rock consists predominantly of volcanic glass, plagioclase feldspars, hornblende, biotite and pyroxene. In some local areas, these phases have been altered to form both montmorilonite and a variety of zeolite minerals such as erionite, clinoptilolite and chabazite.

Karain: Electromicrographs of particles prepared by washing the dust off rock specimens from Karain revealed large numbers of fibres that appear very similar to amphibole asbestos fibres. Further studies showed that these fibres are zeolite materials, which most closely match erionite mineral. There were a number of very small, submicroscopic fibres. Seventy-five percent of the fibers were below 0.25 microns in diameter, and there were quite a large number of longish fibres. The only significant difference in the rock types between Karain and the other control villages were the fibre content of the rock. Table 25 shows chemical analysis of fibres found in rock specimens from Karain with reference data expressed as oxide weight percentages.

Table 25: Average Chemical Analysis of Fibres Found in Rock Specimens Türk 1 and 3, Together with Reference Data Expressed as Oxide Weight Percentages

	Türk 1	Türk 3	Chabazite	Erionite
Al_2O_3	17.6	18.5	23.14	18.90
SiO_2	73.0	72.1	62.57	69.64
CaO	5.6	3.5	12.53	3.54
Na_2O	0.3	0.4	1.25	1.4
MgO	1.0	2.6	—	1.4
K_2O	1.5	1.2	0.77	4.1
TiO_2	0.4	0.4	—	—
MnO	0.1	0.2	—	—
FeO	0.6	1.1	—	—
Al + Sa%	90.6	87.5	85.7	88.54

The raw material from which stucco was prepared and used in the past was examined and found to be essentially free of fibres. A sample of stucco from an old kitchen wall contained some chrysotile either in the stucco or in the cement underneath. This was not found in 3 other stucco samples examined.

Fig. 12 shows electron micrograph of fibres detected in Karain rock sample.

Figure 12. Electron micrograph of Erionite fibres detected in tuff block from the library wall.

Karlık: The rock behind the village was similar to that in Karain and contained mainly calcium-rich fibres. The loosely consolidated rock containing the zeolite fibres was not found. Stucco is rarely used in Karlık. One sample from Karlık contained small quantities of zeolite, calcium-rich, quartz and volcanic glass fibres.

Tuzköy: The majority of the rocks examined contained varying amounts of zeolite fibres. Calcium, quartz muscovite and glass fibres were also detected. Small quantities of short tremolite and chrysotile fibres were detected in two samples of stucco plus cement mixture which was used in the past. In the other twelve geologic samples, zeolite, calcium trisilicate, and calcite and muscovite fibres were detected. The fibres contained in the road dust samples were mainly zeolite. In one sample only very small chrysotile component was detected.

Sarıhıdır: The mass of rock on the south side of the Kızılırmak river is poorly stratified. Specimens taken from the quarry, where much of the building material for the older houses had been extracted, contained a wide range of mineral fibres including zeolite, glass, aluminum silicate chrysotile, tremolite, quartz crocidolite and rutile.

Stucco samples obtained from older houses on both sides of the river contained zeolite, chrysotile, calcium trisilicate and more rarely, tremolite and rutile.

The road dusts on the south side of the river contained a similar range of mineral fibres as those in the quarry. On the north side, substantially fewer fibres were observed, these included chrysotile, glass and quartz.

Airborne Fibres Studies: Karain, Karlık, Sarıhıdır, Tuzköy and Kızılkoy

Airborne levels of respirable (diameter less than 5 microns) and total dust were measured in Karain, Karlık and Tuzköy. More than 150 outdoor samples were collected in the main street, back streets, fields and recreational areas of the 3 villages. Several indoor samples were also taken, particularly in a number of caves attached to the houses, and the walls and floors.

In Table 26, the mass concentrations of respirable dust in the streets of the villages are listed showing the range, number of samples and mean value.

Table 26: Street Samples. Respirable Mass Concentration, mg.m^{-3}

		Range	N	Mean
KARAİN	Main Street	0.2 - 2.8	7	1.14
	Back Street	0.2 - 0.8	6	0.45
KARLIK	Main Street	0.3 - 1.5	3	0.73
	Back Street	< 0.1 - 0.1	4	0.1
SARIHIDIR	Main Street	0.3 - 1.0	6	0.53
	Back Street	0.3 - 0.4	6	0.36
TUZKÖY	Main Street	0.2 - 1.7	6	0.93
	Back Street	0.1 - 1.8	7	0.74
KIZILKÖY	Main Street	0.1 - 0.3	4	0.21
	Back Street	0.1 - 0.2	4	0.13

In Table 27, the corresponding concentration of fibres less than 4 micron together with identification based on compositional analysis are given.

Zeolite fibres make the major contribution to the clouds in Karain, Tuzköy and Sarıhıdır; other fibres included volcanic glass, calcite, calcium phosphate, calcium sulphate, rutile, quartz tremolite and chrysotile.

The size distribution of the fibres are given in Table 28.

In general fibres shorter than 5 microns contributed a similar number of fibres to the cloud as those longer than 5 microns. In two samples from Karain, one from the back street and another from the main street, only short tremolite fibres were observed.

Table 27: Street Samples. Concentration (f/ml) and Identification of Fibres (> 5 micron)

	Range	N	Mean	Identity
KARAİN	0.002 - 0.01	36	0.006	80% zeolite, + calcium oxide sulphate
KARLIK	0.002 - 0.006	21	0.003	20% zeolite, + calcium oxide sulphate
SARIHIDIR	0.001 - 0.029	24	0.009	60% zeolite, + calcite
TUZKÖY	0.005 - 0.025	18	0	85% zeolite, + quartz, glass aluminium silicate
KIZILKÖY	< .001	12	< .001	–

The concentration of these fibres was less than 0.001 fibres/ml.sIn Sarıhıdır chrysotile and tremolite fibres were found in size range smaller than 5 microns contributing up to 10 percent of the fibres in this size range. In Tuzköy, no asbestos fibres were detected, the shorter fibres were mainly zeolite, calcite and muscovite fibres.

Sampling was carried out during the summer time and limited to periods of low agricultural activity when weed control and irrigation were taking place and little or no dust was being generated in the fields. Fibre concentrations were lower than those on the streets (Table 29). Spot samples obtained by vigorously disturbing the soil and sampling the cloud provided no evidence of potentially high fibre concentration.

In the houses, where living rooms were carpeted or had wooden floors and the walls were painted or whitewashed, fibre concentrations were slightly lower than outside. To determine a measure of peak exposure, samples were obtained whilst floor and wall were being cleaned by sweeping. Eleven caves in Karain were sampled in this way and three provided considerably higher concentrations. These fibres were zeolite released from poorly consolidated rock wall (Su Kayası). Eleven caves similarly sampled in Karlık all provided only small concentrations of calcium-rich fibres. In Sarıhıdır similar samples were obtained by sweeping walls and floor of unoccupied houses. Fibre concentrations up to 1 fibre/ml were achieved including zeolite and other aluminium silicates. A small component of tremolite and chrysotile fibres shorter than 5 microns

Table 28: Fibre Size Distribution: Street Samples

Length Micron \ Diameter Micron	< 0.5	0.5 - 1.0	1.0 - 2.0	2.0 - 3.0
KARAİN				
1 - 5	32.4	10.3	2.3	—
5 - 10	2.3	8.4	20.2	1.5
10 - 20	1.5	4.2	8.4	1.5
20 - 30	0.8	1.2	1.5	0.8
30 - 50	0.4	0.4	0.8	0.8
> 50	—	0.4	—	—
KARLIK:				
1 - 5	36.1	11.1	0.5	—
5 - 10	5.8	17.3	12.5	1.0
10 - 20	1.9	3.8	4.8	1.0
20 - 30	0.5	1.4	1.9	—
30 - 50	—	0.5	—	—
> 50				
SARIHIDIR:				
1 - 5	37.1	10.1	3.4	—
5 - 10	2.2	19.1	18.0	1.1
10 - 20	—	3.4	3.3	2.2
20 - 30	—	—	—	—
30 - 50	—	—	—	—
> 50	—	—	—	—
TUZKÖY:				
1 - 5	16.0	7.7	1.3	—
5 - 10	6.4	10.9	30.8	1.3
10 - 20	4.5	2.6	7.7	3.8
20 - 30	0.6	—	1.3	1.9
30 - 50	—	—	1.9	0.6
> 50	—	—	0.6	—

was also detected. Similar concentrations were achieved by sweeping wall blocks in the older houses in Tuzköy, and these fibres were virtually all zeolite.

In the school playgrounds, only in Karain was a fibre concentration significantly greater that obtained from street level during periods of high activity. In Tuzköy, particularly in the oldest and most densely populated region, children playing on the heaps of disused stone blocks created clouds containing up to 0.2 fibre/ml.

Table 29: Work and Recretion Areas: Concentration (f/ml) and Identification of Fibres (< 5 micron)

	f/ml	IDENTITY
KARAİN		
Fields	0.004	Zeolite, glass, calcium silicate
Schoolyard	0.175	Zeolite
Caves (play)	0.050	Calcium, carbonate, sulphate, phosphate
Caves (homes)	0.005 - 0.31	Zeolite
KARLIK		
Fields	0.004	Zeolite, calcium silicates
Schoolyard	0.009	Calcite
Caves	0.005	Calcite
SARIHIDIR		
Fields	0.007	Zeolite, glass, quartz
Schoolyards	0.015	Zeolite, glass, calcium sulphate
Homes	0.005 - 1	Zeolite, glass, aluminium silicates
TUZKÖY		
Fields	0.005	Zeolite, calcite, glass
Schoolyard	0.010	Zeolite, calcium silicate
Homes	0.005 - 0.08	Zeolite, calcite, muscovite

The zeolite fibres in the clouds are frequently seen to be partially splitting longitudinally. To determine the range of fibre dimensions available from the identified sources, samples of respirable dust were dispersed and analyzed.

Size distribution of dispersed respirable fibres in samples of zeolite from Akkuşak quarry, Karain, Tuzköy and Sarıhıdır exhibit a high proportion of fine fibres less than 0.2 microns in diameter. This was particularly high in Tuzköy (75.1%) and in the sample from the Akkuşak quarry (75.7%) which was the main source of building stones for some houses in Karain. Distribution by length was quite similar in the samples from the three villages while a higher proportion of fibres 2 to 4 microns was present in the sample from Akkuşak quarry.

Water Analysis:

Two water samples in Karain, one in Karlık and two in Sarıhıdır were collected and sent to Dr. Millette, Environmental Protection Agency, U.S.A. for analysis of fibre content.

The analysis of water samples gave negative results. In none of the samples was the asbestos, zeolite, or other mineral fibres levels above the detection limit of 50,000 fibres per liter.

Sheep Lung Analysis

Lung specimens from sheep in seven villages located in the area under study were collected in summer 1983. It was not possible to collect sheep lung sample in Karain due to the absence of sheep in this village. The villages from which lung samples were available were Sarıhıdır and Tuzköy in the contaminated area and Boyalı, Bozca, Karlık, Kızılköy and Yeşilöz as control villages. Five or more years old sheep were selected for the study. These sheep were sacrificed and lung tissues, for the mineralogical content analysis, were chosen by F.P., and M.A. and put in formaline. All samples were given random numbers and electron microscope analysis was blindly performed by F.P.

In the majority of samples, the content of zeolite fibres were low. Out of 11 samples in Tuzköy, five had a low but consistent level of fibres while one of the three samples from Sarıhıdır showed the same pattern. Finally, in none of the samples from Karlık, was a lower level of zeolite fibres found. In the other villages, from where no cases of mesothelioma were reported during the study period, none had fibres above the trace level.

On average, the content of chrysotile in the samples was higher than zeolite and crocidolite which was found in very few samples.

Comparing, the average number of fibres of each type in the affected and non-affected villages (Table 30), chrysotile levels were slightly higher in the affected villages while the difference in the same direction was more evident for zeolite fibres. The difference was however not statistically significant.

Table 30: Analysis of the Sheep Lung Content of Fibres

Type of Fibre	Affected Villages*	Non Affected Villages*	t	p
Chrysotile	4.27	3.21	0.562	< 0.7
Zeolite	.13	.01	1.931	< 0.3
Crocidolite	.03	.13	1.633	10.4

* *Average number of fibres per gram* $\times 10^6$

Other Environmental Studies

Tests for aflotoxin on potatoes, bread, grape juice, wine, wheat and fresh fruit by the villagers were negative.

Cyclohexane extracts of soil, dust, and stucco were negative for benzpyrene.

Nitrosamine tests on various water samples were negative. No significant radioactivity was found in the village or in the surrounding soil and hills.

RETROSPECTIVE AND PROSPECTIVE STUDIES

For the period up to 1970, elderly residents and the village headman were our main sources of information as a formal health service had not been established in this region. The health centre in Karain was set up in 1970. Retrospective information was obtained from the records of the health centre, the relatives of patients and the files of those patients who were admitted to the different hospitals.

The incidence of disease was found to be extremely high particularly in 1974 when, in a population of only 604, there were 11 pleural mesotheliomas out of a total of 18 deaths. This fact is illustrated in Table 31 and 32.

The comparison of deaths with neighbouring villages for the year 1974 is shown in Table 33.

The photofluorograms (70 mm. films) taken by the mobile team of the Tuberculous Control Unit in 1971 were reviewed and the findings are shown in Table 34. The results indicate that there has been no significant change in the pattern of chest disease in the village since 1971.

A prospective study was done between January 1975 to January 1981 and 38 cases of malignant pleural mesothelioma were collected. Table 35 shows this study.

Table 31 : Deaths due to Malignant Diseases in Karain (1970 - 75)

		Death from Malignant Desaese			
Year	Population	Male	Female	Total	Mean Age
1970	808	3	5	8	55
1971	795	3	1	4	48
1972	656	4	1	5	49
1973	656	1	2	3	50
1974	604	8	6	14	50

Table 32: Cause of Death

Year	Pleural Mesothelioma	Lung Cancer	Cancers of the G.I.System*	Non - Malignant Diseases**	Total
1970	6	1	1	2	10
1971	2	1	1	5	9
1972	3	1	1	7	12
1973	2	0	1	3	6
1974	11	0	3	4	18

* *May have included peritoneal mesotheliomas*

** *Infantile deaths, cardiovascular disease, and accidents.*

We collected 24 cases of malignant pleural mesothelioma in Karain between the years of 1970 to 1974, and a further 38 cases between 1975 to 1981, A total of 62 cases were thus encountered in this small village over an eleven years period. The disease was seen in both males and females. The average age was 15-20 years lower than that cited in the literature.

Genealogical surveys suggested that blood-relationship was not a necessary prerequisite for the incidence within families. The information pointed to a common environmental etiology.

In the prospective study we also observed that houses in certain parts of the villages had cancer cases. Fig. 13 shows the plan of Karain village with the houses with cancer cases marked. Nearly all these cancer houses had loose volcanic tuff rocks, that is "Su Kayası", which has erionite fibres.

Amongst the female patients with mesothelioma, there were 2 women who had been born and brought up in Ürgüp and Aksalur and who had lived in Karain for more than 25 years. In addition, there was a female patient living in Karain since her marriage who had spent her childhood in Ürgüp.

As we mentioned in Table 33, there were two more female patients living in Yesiloz and Boyali who spent their childhood years in Karain. Figs. 14 and 15 show chest x-rays of a patient from Yesiloz.

In one female patient, breast cancer was discovered and treated surgically. In two patients with skin cancer, one had rapidly progressive deep skin lesion on the right maxilla and he died shortly afterwards. The other female had cancer of the lip.

There was one male patient with suspected laryngeal carcinoma who refused further investigation.

Table 33: Comparison of Deaths in Karain and Neighbouring Villages, 1974

Village & Population	Distance (Kms)	Total No. of Deaths		Causes of Deaths			
		Obs.	Exp.	M.P.M.*	GI.Dis.	Inf.	Others
Karain, 604	0	18	6.60	11	3	1	3
Akçaören, 504	20	11	5.94	0	2	9	0
Akköy, 972	9	6	10.62	0	0	2	4
Başdere, 2,764	13	28	30.19	0	4	13	11
Boyalı,** 530	3	3	5.79	0	1	1	1
Demirtaş, 275	12	3	3.00	0	1	1	1
İltaş, 348	9	2	3.80	0	1	0	1
Karlık, 645	4	5	7.04	0	1	2	1
Yeşilöz, *** 641	7	4	7.00	0	0	2	2

* *M.P.M.: Malignant pleural mesothelioma*

** *One patient from Boyalı died of MPM in 1976. She was a native of Karain and lived there until she was 25 years old.*

*** *A patient migrated to Yeşilöz from Karain when she was 12 years old. She was found to have mesothelioma in 1976, aged 52.*

During the prospective study period we detected cases of chronic benign mineral fibre-induced pleural diseases. Data about them is illustrated in Table 36.

Case 1 stated that he was diagnosed as left sided pleural effusion when he was 20 years old. Fig. 16 shows his chest x-ray. During thoracotomy both pleura were found thickened like leather, and there were scattered hyalinized and calcified plaques. Round atelectasis was also diagnosed in one case. There were two more cases with diffuse pleural thickening and calcification who refused hospital admission for further investigation.

Table 34: A Comparison of Radiological Findings (70 mm films) on Mass Survey in 1971 and 1975

	Number of Cases	
Findings	1971	1975
Diffuse lung fibrosis	21	24
Pleural tumour	7	5
Tuberculosis	7	3
Lung Ca.	4	0
CPP resemble asbestos - related disease	2	2
Calcification	2	2
Pleural thickening	0	3
Films Taken	564	452

** CPP - Calcified Pleural Plaques*

Table 35: Prospective Study of New Patients in January 1975 and 1981 (Population 800 - 500)

		Sex		Age			
				Male		Female	
Diseases	Total	M	F	Range	Mean	Range	Mean
M.P.M.	38	20	18	27 - 65	44.9	37 - 67	50.8
Gastric Ca.	4	1	3	46		34 - 70	53.6
Bronchial Ca.	2		2	—		40 - 65	52.5
Skin Ca.	2	1	1	80		65	
Breast Ca.	1	—	1	—		57	
CPP* and/or CFP**	7	— 5	— 2	— 54 - 64	52	50 - 60	55

M = Male

F = Female

** Calcified Pleural Plaques*

***Chronic Fibrosing Pleuritis*

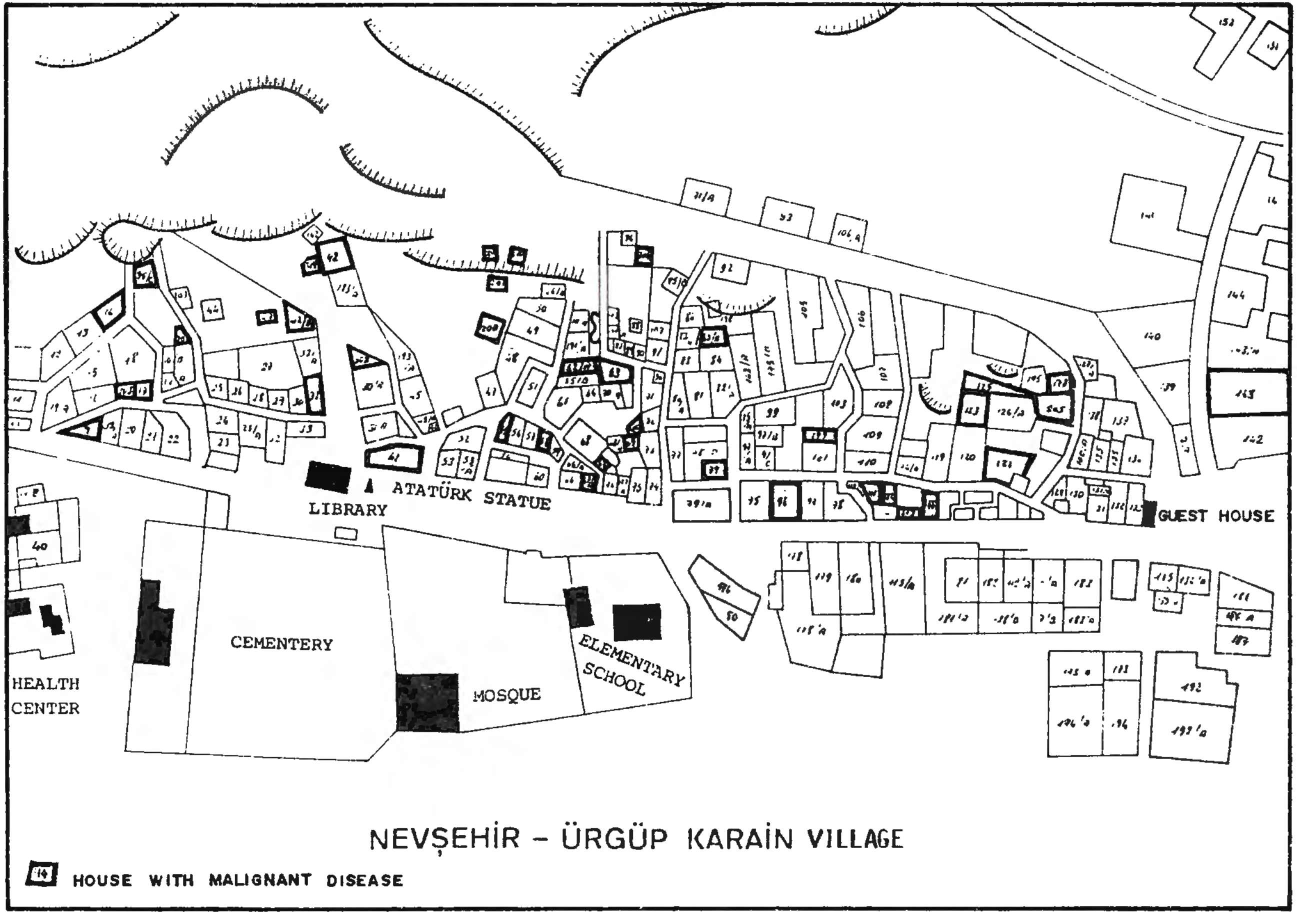

Figure 13. Plan of Karain village showing the houses (shaded) of the patients with mesothelioma.

Table 36: Information About Cases of Benign Pleural Diseases in Karain

Case	Age/Sex	Clinical Radiological Findings	Diagnostic Methods	Dx.	Follow - up (Years)
O.D.	45/Male	Left pl. effusion more than 20 years	Thoracotomy	CFP* Pl. Eff.	6
O.K.	55/Male	Right Pleural thickening and calcification	Clin - radiol	CFP	6
M.C.	65/Male	Right pleural thickening and calcifacation. Ascitis	Clin - radiol Laparoscopy	CFP Active Hepatitis	5 died
H.A.D.	45/Male	Right hydropneumothorax	Pl. Punch Biopsy	CFP Pl. Eff.	6
A.O.	45/Male	Left pl. thickening and lung fibrosis	Clin - radiol	CFP	6

** CFPl : Chronic Fibrosing Pleuritis.*
***Pl. EFF. : Pleural Effusion.*

Figure 14. First chest x-ray of a female patient from Yeşilöz village who spent her childhood in Karain: Malignant Pleural Mesothelioma.

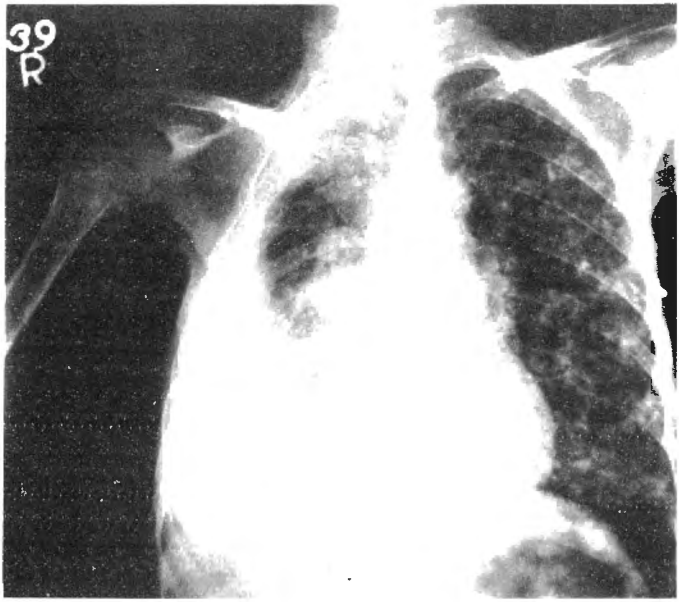

Figure 15. Second chest x-ray of same female patient showing widespread bone and lung metastases after one year.

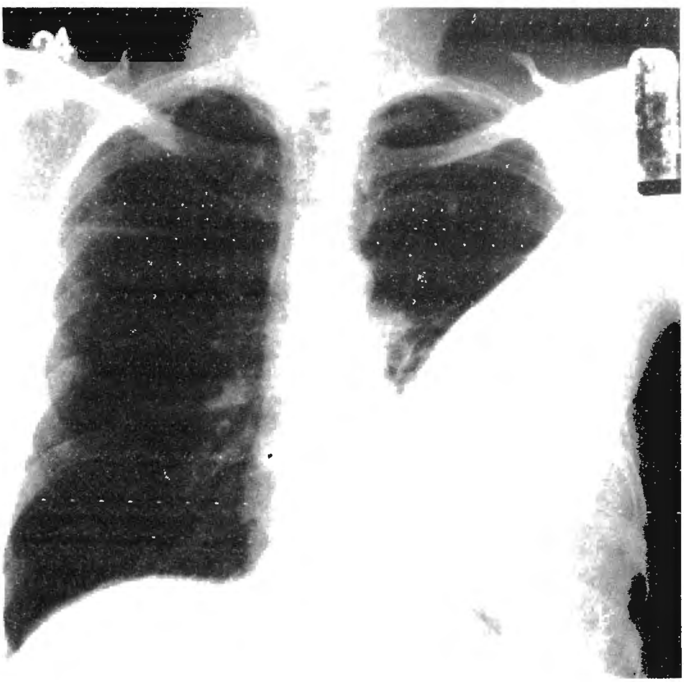

Figure 16. Erionite related left sided benign pleural effusion in a patient from Karain.

RADIOLOGICAL SURVEY

Radiological screening of Karain and Karlık was done twice in 1978 and 1979 with a portable x-ray machine.

Standard chest x-ray findings in villagers aged more than 20 years old is shown in Table 37.

Table 37: Chest X-Ray Findings in Villagers Above 20 Years Old in Karain and Karlik

Radiological Findings	Karain				Karlık			
	Male: 149		Female: 176		Male: 107		Female: 116	
	%	No	%	No	%	No	%	No
Pl. Thickening	22.8	(34)	9.7	(17)	21.5	(23)	6.9	(8)
Pl. Effusion	1.3	(2)	–	–	–	–	–	–
Pl. Thick-Calci.	2.7	(4)	0.6	(1)	0.9	(1)	–	–
Pl. Plaque	0.7	(1)	–	–	–	–	–	–
Pl. Eff. - thick.	2.7	(4)	0.6	(1)	0.9	(1)	–	–

Although radiological screening suggested one case of mesothelioma in Karlık, it was not proved. Our retrospective and prospective studies did not show any cases of mesothelioma in Karlık.

Mineralogical study in the lung tissues was initially requested from Department Physique-Biologie Laboratoire du Centre d'Etudes et Recherches des Charbonages de France. First report for one of our patients with chronic fibrosing pleurisy (Case 1, in Table 35) revealed 1.2×10^5 chrysotile and 3×10^5 amphibole asbestos fibres per gram of dry lung tissue. This findings was not compatible with the environmental studies. Later on it was revealed that formalin solution for preservation of the tissues was contaminated with asbestos. Some of the remaining lung tissue of this patient was sent to the Environmental Sciences Laboratory, Mount Sinai School of Medicine, U.S.A. and they demonstrated the presence of both asbestos and erionite fibres. Approximately 90 per cent of the fibrous particles in the lung tissues consisted of sodium-potassium-calcium aluminosilicates, a composition consistent with that of erionite. A smaller amount (approximately 1 to 5 per cent by volume) of fibrous mineral was identified as tremolite*.

Postmortem lung biopsy was taken from a 25-year-old male patient with malignant pleural mesothelioma and sent to both France and U.S.A. through Sweden * *. According to the report of P. Sebastien from Laboratoire D'Etude Des Particules Inhalees, France, there were 530 ferruginous bodies and 2×10^7 uncoated fibres per gram of dry lung tissue. Fibrous mineral phases and proportions on a numerical basis (%) was: Zeolite (61%), Calcium silicate (18%), tremolite (11%), unidentified (10%). The dimensions of fibres were: Mean length 5.5 microns, diameter 0.19 micron; proportion of fibres longer than 8 micron and thinner than 0.25 micron: 10%. This patient was born and brought up in Karain and he left the village after finishing his elementary school education. After getting his diploma in pharmacy he joined the army for his military service. He was diagnosed as malignant pleural mesothelioma in the military academy hospital and discharged from the army. After that he went to Stockholm to seek medical advice. His postmortem lung tissue was sent to Environmental Sciences Laboratory, Mount Sinai School of Medicine, U.S.A. The composition of fibrous minerals of his lung tissue was 64 percent zeolites, 27 percent amphibole and 9 percent chrysotile fibres*.

The third case of malignant pleural mesothelioma whose lung tissue was also submitted for mineralogical study was a 38-year-old male patient. He was born and lived in Karain until finishing his elementary school. From 1954 to 1966 he lived in other parts of Anatolia. He immigrated to Sweden in 1966 and worked in various restaurants until 1976 when he started working as a butcher. He complained of dull pain in the left side of his chest and was diagnosed as malignant pleural mesothelioma by thoraco-

* *Rohl, A.N. et al.: Endemic Pleural Disease Associated with Exposure to Mixed Dust in Turkey. Science, 216: 518, 1982.*

***Boman, G., et al.: Malignant Mesothelioma in Turkish Immigrants Residing in Sweden. Scand. J. Work. Environ. Health, 8: 108, 1982.*

tomy. Specimens of the pleura and lung were submitted for mineralogical study to the Environmental Science Laboratory, Mount Sinai School of Medicine, U.S.A. The percentages of fibrous minerals present in lung tissue were as follow: Zeolites 75%, Amphibole 9%, Chrysotile 5%, others (pyroxen ?) 5%.

FERRUGINOUS BODIES IN THE SPUTUM OF ZEOLITE VILLAGERS

Ferruginous bodies in sputum samples from inhibitants of both mesothelioma villages (Karain-Tuzköy) and their control villages (Karlık-Kızılköy) was evaluated as biological monitoring*.

The counts of ferruginous bodies in sputum samples from inhibitants of Karain and Tuzköy, increased with the subjects' age whereas 94% of samples collected in the control village were free of ferruginous body. Fig. 17 shows erionite fibres in the lung washing fluid of a person from Karain.

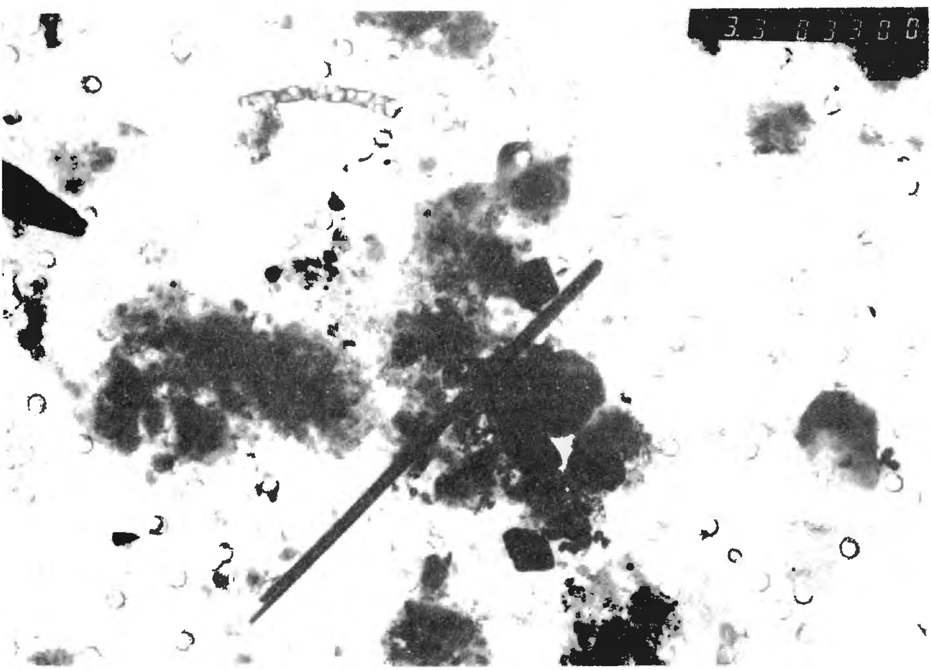

Figure 17. Erionite fibre in lung washing fluid of a patient from Karain.

* *Sebastien, P., et al.: Ferruginous Bodies in Sputum as an Indication of Exposure to Airborne Mineral Fibres in the Mesothelioma Villages of Cappadocia. Arch. Envir. Health; 39: 18, 1984.*

EXPERIMENTAL STUDIES IN ANIMALS

Inhalation Exposure: Groups of 20 male and 20 female Fischer 344 rats were exposed to inhalation of 10 mg/m3, respirable range Oregon erionite, or synthetic non-fibrous erionite or UICC crocidolite for 7 hours per day, five days per week for one year and were compared to 20 male and 20 female unexposed animals. Pleural mesotheliomas were observed in 27/28 erionite-exposed rats surviving more than 12 months. One pulmonary squamous carcinoma and one mesothelioma were observed in 28 rats exposed to synthetic non-fibrous erionite and one pulmonary squamous carcinoma was found in UICC crocidolite exposed rats. No such tumours were observed in the 28 controls*.

It was noted that these erionite-induced pulmonary tumours in rats had a similar ultrastructural appearance to mesothelioma induced by direct inoculation into the pleural and peritoneal cavities**.

Intrapleural Administration: Groups of 20 male and 20 female Fischer 344 rats, approximately 60 days old, received an intrapleural injection of 20 mg of either Oregon, U.S.A. erionite, Karain, Turkey rock fibre, non-fibrous zeolite or chrysotile asbestos in 1 ml saline and saline alone. The fibres for inoculation were collected from airborne sample in the inhalation chamber. The per cent of fibres more than 4 microns in length were: Oregon erionite - 40.7%, Karain rock fibres 10.6%. The rats were observed for their life-time. The incidence of pleural mesothelioma was 40/40 Oregon erionite-treated, 38/40 Karain rock fibre-treated, 2/40 non-fibrous zeolite treated, 19/40 chrysotile asbestos rats and 1/40 control rats*.

* *Wagner, J.C., et al.: Erionite Exposure and Mesothelioma in Rats. Br. J. Cancer, 51: 727, 1985.*

** *Johnson, N.F., et al.: Pluripotential Nature of Mesotheliomata Induced by Inhalation of Erionite in Rats. Br. J. Exp. Pathol., 65: 377, 1984.*

TUZKÖY - GÜLŞEHİR/NEVŞEHİR RESEARCH

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Tuzköy is located about 40 kms northwest of Karain and has a population of 3,000. Most of the villagers like those in Karain, work in agriculture and breed livestock. Some of them work in a nearby salt mine. Localization of Tuzköy and its control village Kızılkoy are shown in Fig. 11.

We were informed that more than 60 villagers died of malignant disease between the years 1971 and 1977 and we decided to study the possible etiology.

The Institute of Mineralogic Research and Exploitation of Turkey had shown that Tuzkoy and its vicinity was a volcanic area covered with volcanic sediments, which were usually 300 m. thick tuffs. These findings were also confirmed by the Faculty of Earth Sciences, Hacettepe University, Ankara, Turkey.

Two epidemiological studies were carried out in Tuzköy in the years 1978 and 1981. The results of the environmental studies have been mentioned in the Karain Research.

EPIDEMIOLOGICAL STUDY

First Epidemiological Study: The study was done in 1978. At that time the population of Tuzköy was 2,919. Kızılköy which was selected as a control village and was just 12 kms. south of Tuzköy. The population of Kızılköy was about 631.

In both villages, persons who were aged 25 years or more were selected and divided by sex and age into groups. Using the stratified sampling method, we determined the number of persons from each group that should be included in the study. Three hundred and thirty one persons (153 males and 178 females) from Tuzköy, and 100 persons (47 males and 53 females) from Kızılköy were randomly selected. Of these, 19 patients from Tuzköy and 5 from the control village did not participate in the study. Thus, 312 persons (145 males and 167 females) from Tuzköy and 95 (45 males and 50 females) from the control villages were investigated. No significant difference was found between the original and final groups selected from each village ($P > 0.05$). Tables 38 and 39 show the distribution by age and sex of the people studied in Tuzköy and Kızılköy.

A questionnaire that included smoking habits, medical history, and family history was filled out for each person. This was followed by a physical examination and all positive findings were recorded. P.A. chest x-rays were taken with a portable Picker x-ray machine. Chest x-ray films were independently interpreted by M.A. and Y.I.B.

Table 38: Distribution by Age and Sex of Participants from Tuzköy

	No. (%) of Participants	
Age/Groups; Years	Males	Females
25 - 39	62 (43.0)	82 (57.0)
40 - 54	42 (42.9)	56 (57.1)
55 - 69	30 (57.7)	22 (42.3)
More than 70	11 (61.1)	7 (38.9)
TOTAL	145 (46.5)	167 (53.5)

Table 39: Distribution by Age and Sex of Participants from Kızlılköy

	No. (%) of Participants	
Age/Groups; Years	Males	Females
25 - 39	19 (42.2)	26 (57.8)
40 - 54	12 (44.4)	15 (55.6)
55 - 69	11 (57.9)	8 (42.1)
More than 70	3 (75.0)	1 (25.00)
TOTAL	45 (47.4)	50 (52.6)

Results: The mean ages of the people in the Tuzköy and control village (Kızılköy) study groups were, 42.83 ± 13.82 and 42.52 ± 14.69 years respectively, are not significantly different ($P > 0.05$). The differences between the mean ages of the male and female participants in both villages were also not significant.

Three patients in the group from Tuzköy were admitted to the Hospital of Hacettepe University.

Case 1: A 42-year-old male farmer, complained of weakness and malaise. Physical and radiological examinations revealed left sided pleural effusion with calcified pleural plaques. Pleural biopsies taken by Abram's needle revealed chronic fibrosing pleuritis. A left thoracotomy was performed, during which 1,300 ml. hemorrhagic fluid was aspirated. The pleura was thickened into plaques on which 5 nodular tumors were located. All tumours were excised, and lung biopsies were taken. A mixed type malignant pleural mesothelioma was diagnosed.

Case 2: A 31-year-old salt miner, complained of dyspnea and chest pain on the left side. Physical and radiological examination revealed left sided pleural effusion. Histologic examination of pleural needle biopsies showed malignant pleural mesothelioma.

Case 3: A 38-year-old man complained of right sided chest pain. Physical and radiological examination revealed diffuse right sided pleural thickening (Fig. 18). He had thoracotomy, and decortication was performed. Histological examination revealed chronic fibrosing pleuritis. Some biopsies which were subjected for mineralogical study revealed erionite fibres in the lung tissue.

Information on 6 patients who died in Tuzköy between 1977 and 1978 is given in Tablo 40.

Table 40: Information on 6 People Who Died in Tuzköy Between July 1977 and February 1978

Cases	Sex	Age at Death	Cause of Death
H.C.	F	66	Peritoneal mesothelioma
A.I.D.	M	59	Lung cancer
D.T.	F	58	Cirrhosis
H.C.	F	62	Peritoneal mesothelioma
E.C.	F	64	Peritoneal mesothelioma
I.Y.	M	45	Chronic pyelonephritis

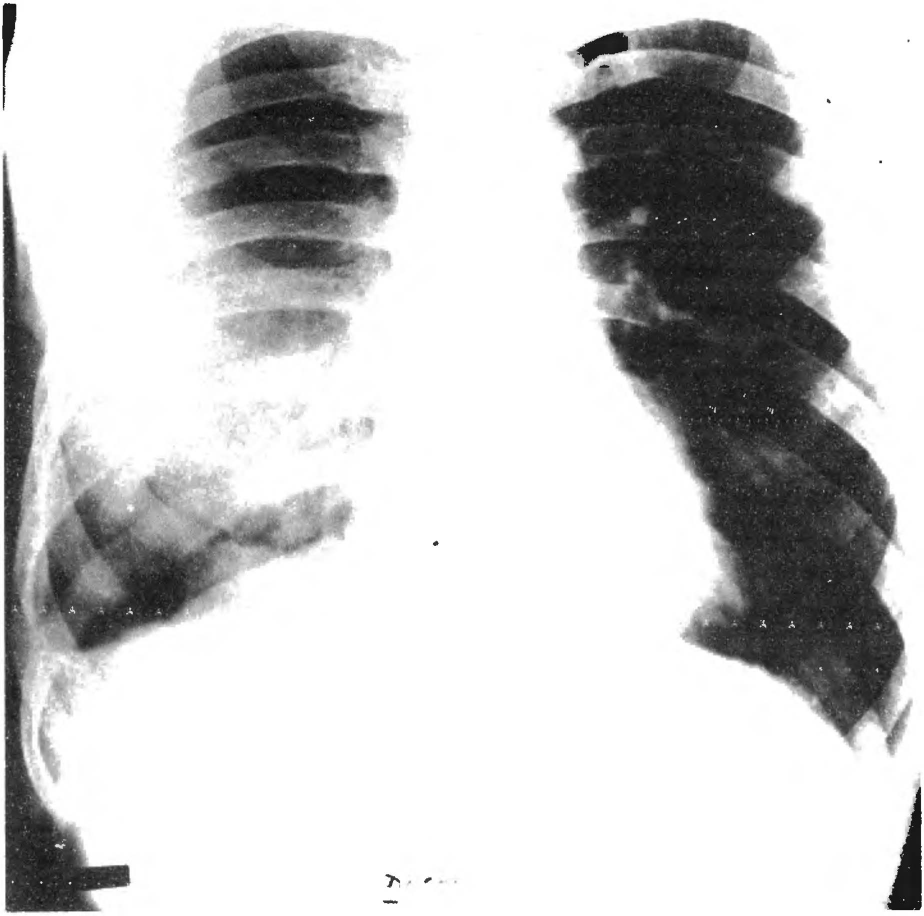

Figure 18. Chest x-ray of a patient from Tuzköy showing diffuse pleural thickening on the right side.

There were 8 patients who were still alive in Tuzköy. Six of them were diagnosed as malignant pleural mesothelioma, one chronic fibrosing pleuritis and one with skin cancer.

No case of malignant disease was seen in the control village and chest x-ray indicated no pathologic conditions.

The result of the radiological screening is shown in Table 41.

Table 41: Chest X-Ray Findings in the Randomly Selected 312 Persons Aged more than 25 Years in the Tuzköy Survey

Abnormalities	Number	%
Calcified pleural plaques	53	17
Pleural thickening	33	10.5
Small opacities	38	12.5
Obliteration of C - D angle	47	15
(Two of them were diagnosed as mesothelioma)		

Second Epidemiological Study: The second epidemiological study in Tuzköy and its control village (Kızılköy) was done in 1981. This study presents pleuro-pulmonary radiological findings, as well as the causes of deaths in both villages for the previous 3 years.

The total population for Tuzköy and Kızılköy were 2,919 and 631, respectively. Study groups were selected by the stratified sampling method; only individuals who were at least 25 years of age were included. Tuzköy and Kızılköy study groups thus consisted of 145 males and 167 females and 45 males and 50 females respectively.

A questionnaire that included history of present and past illness, smoking habits and family history was completed by a chest physician for each participant. Results of physical examinations were recorded for each subject. Standard chest x-rays were taken with a portable Picker x-ray machine. Microfilms which were taken in 1972 and 1975 were also examined and evaluated independently.

Most patients from soth villages were surveyed as in-patients at the Hacettepe University Hospital. Some were patients in other hospitals and a few were out patients or were surveyed in their homes. The number of deaths in those aged 15 years or more in both villages were recorded from January 1, 1978 to December 3, 1980.

Results: Distribution of the jobs of investigated persons in the villages are shown in Table 42.

Table 42: Distribution of the Jobs of Investigated Persons in Tuzköy and Kızılköy

	Tuzköy		Kızılköy	
Occupation	No.	%	No.	%
Farmer	49	15.71	41	43.16
Salt miner	44	14.10	0	0.00
Civil servant	16	5.13	2	2.10
Housewife	167	53.52	50	52.64
Others	36	11.54	2	2.10
TOTAL	312	100.00	95	100.00

Table 43 shows radiological findings and in different age groups.

Table 43: Relation of Age Groups to X-Ray Findings

	CPP		PT		OCPA		DIPF	
Age/Group	No.	%	No.	%	No.	%	No.	%
25 - 39 yr	8	5.5	7	7.8	10	6.9	1	0.6
40 - 54 yr	12	12.2	5	5.1	15	15.3	15	15.3
55 - 69 yr	24	46.1	18	34.6	18	34.6	15	28.8
70 + yr	9	50.1	3	16.6	4	22.2	7	38.8

CPP = Calcified Pleural Plaques
PT = Pleural Thickening
OCPA = Obscured Costophrenic Angles,
DIPF = Diffuse Interstitial Pulmonary Fibrosis

Table 44 shows the relation of radiological findings with occupation.

Table 44: Relation Between X-Ray Findings and Occupation in Tuzköy

	CPP		PT		OCPA		DIPF	
Occupation	No.	%	No.	%	No.	%	No.	%
Farmer	14	28.5	11	22.4	15	30.6	10	20.4
Salt miner	12	27.2	9	20.4	12	27.3	4	4.0
Civil servant	3	18.7	1	6.2	3	18.7	2	12.5
Housewife	14	8.3	2	1.1	11	6.5	17	10.1
Others	10	27.7	10	27.7	6	16.6	5	13.8

CPP = *Calcified Pleural Plaques*
PT = *Pleural Thickening*
OCPA = *Obscured Costophrenic Angles*
DIPF = *Diffuse Insterstital Pulmonary Fibrosis*

Relation of radiological abnormalities with smoking habits is documented in Table 45.

Table 45: Relation Between the X-Ray Findings and Smoking Habits in Tuzköy

	CPP		PT		OCPA		DIPF	
Smoking Habits	No.	%	No.	%	No.	%	No.	%
Nonsmoker	30	14.2	11	5.2	20	9.5	22	10.4
Ex - smoker	5	38.4	6	46.1	7	53.8	2	15.1
Smoker	18	20.2	16	17.9	20	22.4	14	15.7

CPP = *Calcified Pleural Plaques*
PT = *Pleural Thickening*
OCPA = *Obscured Costophrenic Angles,*
DIPF = *Diffuse Interstitial Pulmonary Fibrosis*

The results of mortality study during past 3 years is shown in Table 46.

Table 46: Mortality Study in Tuzköy, January 1, 1978 - January 1, 1981, (Population 3.000)

				Age			
		Sex		Male		Female	
Diseases	Total	M	F	Range	Mean	Range	Mean
M.P.M.*	15	6	9	33 - 58	44.5	28.64	47.5
M.PE.M.**	12	4	8	48 - 60	55.5	42.68	51.7
Bronch. Ca.	8	7	1	44 - 60	55		54
Extra.Pul.Ca.	6	5	1	(4 GI; 1 larynx; 1 leukemia)			
Non-tumoral (CHF., COLD., CVD)	26	18	8	41 - 75	61.6	19.80	64.5

* *M.P.M. = Malignant Pleural Mesothelioma*

** *M.PE.M. = Malignant Peritoneal Mesothelioma*

MINERALOGICAL STUDIES IN LUNG TISSUES

The first mineralogical study in the lung tissue was done by Pooley and showed erionite fibres compatible with environmental zeolite inhalation. Fig. 19 shows erionite fibres in the lung tissue of a patient with chronic fibrosing pleuritis, compatible with environmental zeolite inhalation.

Subsequently Sebastien et al performed mineralogical studies in two cases of malignant mesothelioma from Tuzkoy. The findings in these patients were shown in Tables 47 a and b.

**Sebastien, P et al.: Zeolite Bodies in Human Lungs from Turkey. Lab. Invest., 44: 420, 1981.*

Figure 19. Scanning electron microscopic view of erionite fibres in the lung tissue of the case with pleural thickening, (case in Figure 18).

Table 47(a): Numerical Concentrations and Length Characteristics of Lung Fibres Detected in Two Cases of Malignant Mesothelioma from Tuzköy
Case 1: 42 - year - old female, D.Y.
Case 2: 52 - year - old male, S.M.

	Examination with LM		Examination with TEM			
	Ferruginous bodies		Uncoated Fibres		Uncoated Erionite	
	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2
Number counted	144	121	7	15	111	90
Numerical concentration (number per gm. of dried lung)	1.7×10^4	1×10^4	Not calculated		1.9×10^8	1.7×10^8
Length (micron)						
Mean	34	43	5.4	8.1	4.1	3.4
Std. deviation	21	21			2.3	2.0
Maximum	108	90	27	16	9.6	8.8

Table 47(b): Chemical Characteristics of Fibres

Sample	Na_2O	MgO	Al_2O_3	SiO_2	K_2O	CaO	FeO
Ref. erionite	3	0.8	19.4	69.1	4.2	4.2	
Ref. erionite		1.6	17.9	71.7	3.1	3.5	1.5
Erionite lung							
Fibres (uncoated)	1.6		20.3	71.9	4.1	0.8	0.5
Central core of coated fibres	0.8	0.1	18.9	73.3	4.9	0.8	0.7

Fig 20 shows Zeolite Body in the lung in a patient from Tuzköy.

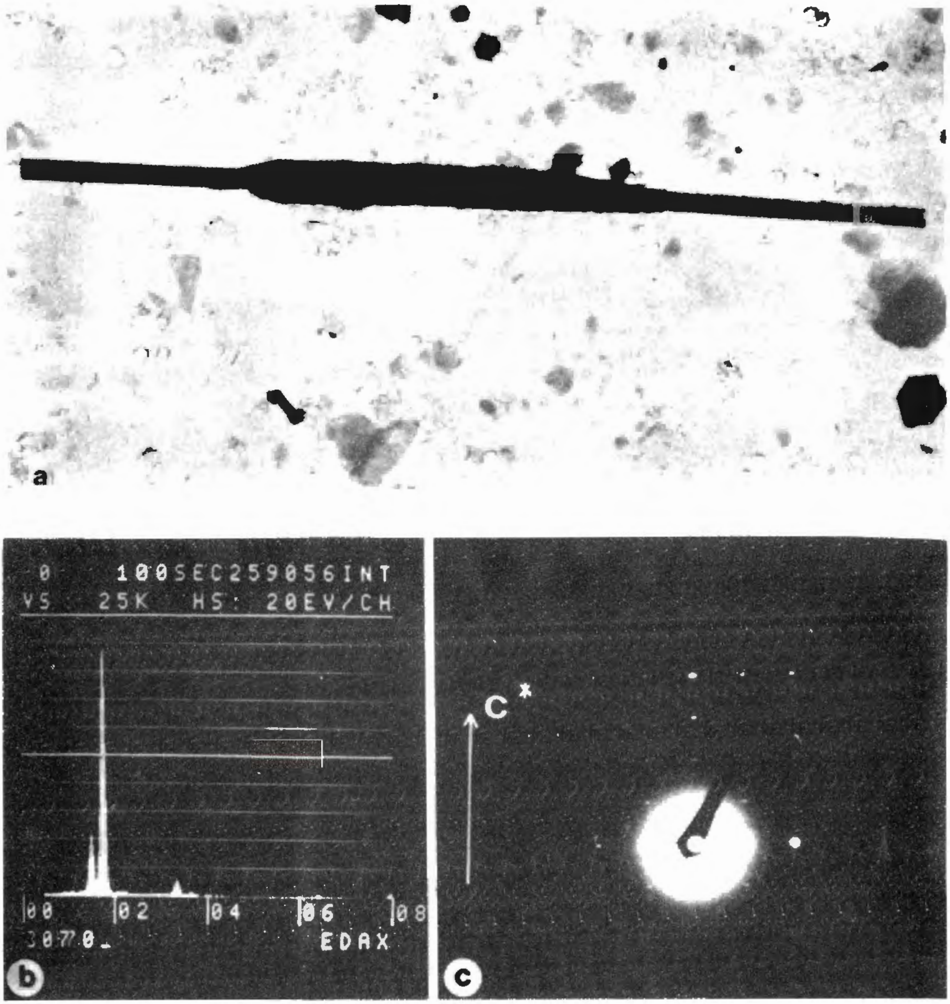

Figure 20. Zeolite body. Characterization of the contral core of a zeolite (erionite) body in the lung using the ATEM. a. Morphologic featuresi b. Typical EDS Spectrumi c. SAED pattern showing (0002) and (1120) erionite reflections. Figure 20a, x 5-200.

(From: Sebastien, P., Gaudichet, A., Bignon, J., and Barış, Y.I.: Zeolite Bodies in Human Lungs from Turkey. Lab.Invest., 44:420, 1981. By the U.S.-Canadian Academy of Pathology)

SARIHIDIR - ÜRGÜP/NEVŞEHİR RESEARCH

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Sarıhıdır is located 13 kms. north of Karain and 24 kms. east of Tuzkoy (Fig. 11). The village has a population of 900 and most of the villagers work in agriculture and breed live stock.

Sarıhıdır was located in the south bank of Kızılırmak river up to 1960. Because of floods, the villagers moved to the northern bank of the river and established a new village there. Only a few houses were left on the southern side of the river. The old houses were built of volcanic tuff rocks while most of the new houses were constructed with bricks and/or concrete.

After Mumpton's and Ataman's report concerning the finding of fibrous zeolite deposits in the south part of the village, an epidemiological and case control study was carried out in the village.

EPIDEMIOLOGICAL AND CASE CONTROL STUDY

Both male and female villagers above 25 years of age were selected for the study. A questionnaire which covers, identification, chief complaints, present history, past and family history was filled out for 306 villagers. Afterwards a physical examination was done and the positive findings were recorded. P.A. chest x-rays were taken with a portable Picker x-ray machine and the films were interpreted independently by Y.I.B., and M.A.

Results: The abnormal radiological findings of persons from Sarihidir is shown in Table 48.

Seven patients (3 with mass lesions, 2 with pleural effusion and one each with diffuse lung fibrosis and diffuse pleural calcification) were admitted to the Hacettepe University Hospital for further investigation.

Table 48: Chest X-Ray Findings of 196 Patients Over 25 Years of Age from Sarıhıc

Findings	No.	%
Diffuse Lung Fibrosis	131	66.83
Pleural Thickening	41	20.91
Calcified Pleural Plagues	19	9.69
Mass	3	1.53
Pleural Effusion	2	1.02
TOTAL	196	100

Two patients with pleural effusion (male and female) were diagnosed as malignant pleural mesothelioma following a biopsy using Abram's needle biopsy. The female patient underwent thoracotomy and a successful pleuro-pneumonectomy was done. Mineralogical study in the lung tissue was carried out (Case 1).

Three patients with tumoural mass were investigated. Epidermoid bronchial carcinoma was diagnosed by thoracotomy in the first patient. He was a heavy smoker and he had extensive hyalinized and calcified pleural plaques. In the second male patient, there was a mass with calcified pleural plaques on the right side (Fig. 21). He was operated on and diagnosed as localized malignant pleural mesothelioma. Mineralogical study in the lung tissue was done (Case 2).

The last patient with tumoural mass was a middle aged female. She complained of vague right sided chest pain, and a chest x-ray showed a round mass with a smooth border suggesting hydatid cyst (Fig. 22). She was operated on and a hamartoma of the lung was diagnosed. Mineralogical study in the lung tissue was also done (Case 3).

One middle aged male patient with extensive pleural calcification was admitted to the hospital. He was asymptomatic, and both clinical and laboratory studies including complete pulmonary function tests were found to be normal. Fig. 23 shows his chest x-ray.

The last patient who was admitted to the hospital was a 63-year-old male. He had been healthy until 7 years previously when he began to experience dyspnea during exertion. This slowly progressed and at the time of admission, he was becoming dyspnoeic after minimal effort. He complained of a cough, especially in the morning, with scanty sputum.

The patient was born and had lived all his life in Sarıhıdır/Cappadocia region. Although his main occupation was farming, he had also been cutting building stones for houses for nearly 20 years, for about 20 days annually. The stones were originally large volcanic tuffs. Until recently, he habitually smoked 1.5 packets of cigarettes daily.

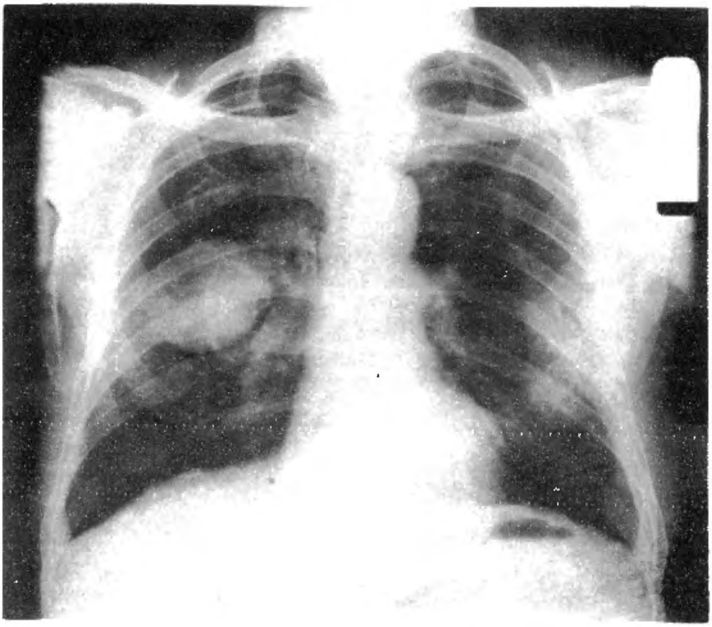

Figure 21. Radiographs showing right sided mass with bilateral pleural and diaphragmatic calcification. Malignant mesothelioma from Sarıhıdır.

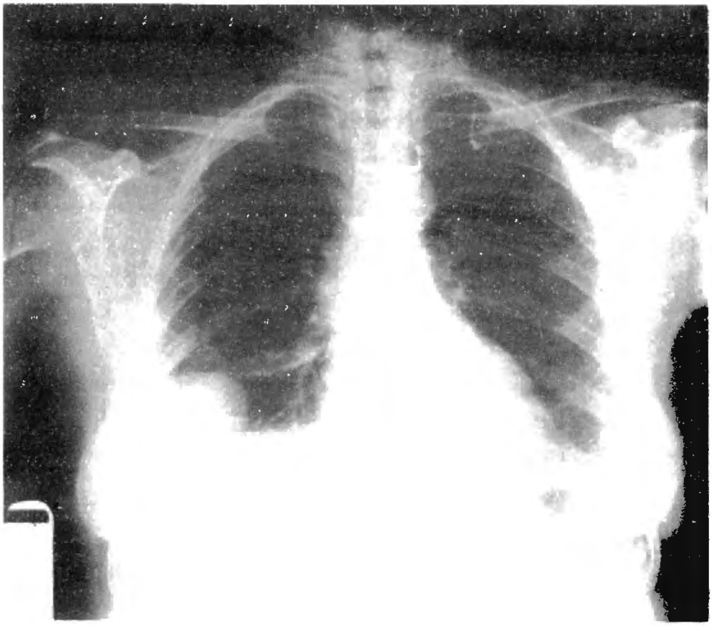

Figure 22. Radiograph showing a mass on the right lower lobe. Hamartoma of the lung in a patient from Sarıhıdır.

Figure 23. Radiograph showing bilateral diffuse calcified pleural plaques with pleural thickening. Case from Sarıhıdır.

Physical examination revealed a dyspneic old man with a barrel shaped chest. Breath sounds were diminished and scattered rhonchi and diffuse late inspiratory rales were heard over the middle and lower lung fields. There was stage 2 clubbing of the fingers and toes with cyanosis. The edge of liver was felt 3 fingerbreaths below the right costal margin and it was slightly tender.

The chest x-ray is shown in Figure 24. The gram stain of the sputum showed some neutrophils and epithelial cells and culture yielded normal flora but no acid-fast bacilli were found. PPD skin test with 1 IU was positive. ESR was 3 mm/hr (Westergren): latex fixation test, ANA and LE cell tests were all negative. An ECG showed bifascicular block. Arterial blood gas level were pH 7.43, PCO_2 33.2 mmHg, PO_2 71.5 mmHg. Pulmonary function tests showed FEV_1 1.71 Lt. (77% Predicted), FVC 2.99 Lt.

Figure 24. **Chest x-ray showing diffuse fibrosis mainly in the lower lobes; Erionite induced lung fibrosis: Case from Sarıhıdır.**

(96% Predicted), FEV_1/FVC ratio 57%, diffusion test (CO steady state) 14.6 ml/min/mmHg (65% Predicted).

Multiple transbronchoscopic biopsies were taken and the tissues were sent for both histopathological and mineralogical studies. Histological examination revealed mononuclear inflammatory cells, marked thickening of the alveolar walls and interstitial fibrosis with amorphous iron pigment (Case 4).

MINERALOGICAL STUDIES IN LUNG TISSUES

Case 1. R.P., 50-year-old female patient. Malignant Pleural mesothelioma was diagnosed by thoracotomy.

Concentration of Ferruginous Bodies in the Lung Tissue:	4×10^3	per gm of dried lung.
Characterization, sizing and counting of TEM size Fibres:	7×10^7	per gm of dried lung.

Zeolite (85%) Amorphous Glass (15%)
Mean length: 4.8 microns
Mean diameter: 0.31 micron

Case 2. V.C., 45-year-old male patient. Localized Malignant Pleural Mesothelioma was diagnosed by thoracotomy. Concentration of Ferruginous Bodies in the Lung Tissue

Lung Parenchyma	2.6×10^3	per gm. of dried lung
Near Tumour Tissue	1.8×10^3	per gm of dried lung

Characterization, size and concentration of TEM size Fibres:

Lung Parenchyma	1.1×10^8	Zeolite (98%)
Near Tumour Tissue	1.7×10^8	Zeolite (98%)

Mean Length: 4.0 microns
Mean Diameter: 0.27 micron

Case 3. F.G., 35-year-old female patient. Pulmonary Hamartoma was diagnosed by thoracotomy. Concentration of Ferruginous Bodies in the Lung Tissue: 1.9×10^4

Characterization sizing and counting of TEM size Fibres: 6.4×10^8

Zeolite (92%)

Mean Length: 3.7 microns
Mean Diameter: 0.27 microns

Case 4. A.B., 63-year-old male patient. Diffuse lung fibrosis diagnosed by transbronchoscopic lung biopsy. One pulmonary fragment was analyzed for the presence of fibres with analytical transmission electron microscope. Numerous zeolite (erionite) fibres were found in a concentration of 2×10^8 per gram of dried lung. Size characteristics were as follows: mean length 4.8 microns and mean diameter 0.4 micron. Thick fibres up to 1.2 micron in diameter were also present. Beside fibres, particulate matter, including diatom fragments, was abundant (Fig. 25).

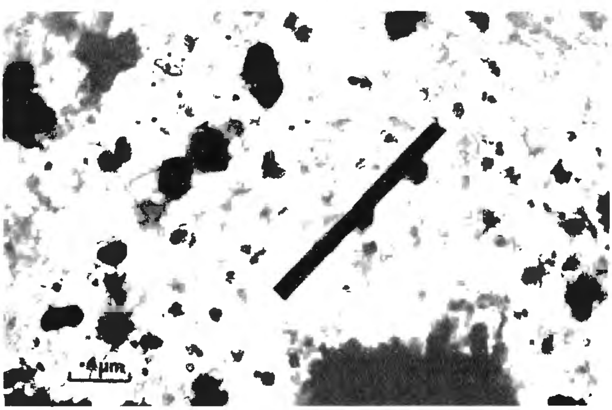

Figure 25. Erionite fibre in the lung tissue of the patient, whose chest x-ray is shown in Figure 24.

CLINICAL EVALUATION OF 94 CASES OF MALIGNANT PLEURAL MESOTHELIOMA COLLECTED FROM ERIONITE VILLAGES

We collected 94 cases of malignant pleural mesothelioma from erionite villages; 62 cases from Karain, 27 cases from Tuzköy, 3 cases from Sarıhıdır and 2 cases from other villages in Cappadocia.

The sex and age distribution of 94 cases were as follows:

Males: 56		Females: 38	
Mean	**Range**	**Mean**	**Range**
50.8	27 - 71	50.2	32 - 69

Symptoms: The mode of onset in all cases was insidious chest pain and the interval before reaching hospital was about six months. The pain usually started as a sense of heaviness and coldness in one side of the chest and shoulder. Severe chest pain with dyspnea was the classical picture in those patients in the terminal stage. Intractable chest pain, which also radiates to the upper part of the abdomen, was usually seen in cases with tumoural involvement of the chest wall. Dyspnea was usually seen in patients who had massive pleural effusion, mediastinal shift and cardiorespiratory failure. Orthopnea, cyanosis and tachypnea were always seen in the late stage. Weight loss was found in most cases. Fever was not detected in any of our cases.

Physical Findings: The most common physical findings were related to pleural effusion and/or pleural thickening. In addition, presence of tumoural mass on the chest wall and bronchial breathing were also detected in some cases. Superior vena cava obstruction and Claude Bernard-Horner's syndrome were observed in two cases respectively. The sunken, immobile chest, the so-called "Frozen Chest" was a definite finding in advanced cases.

Severe chest and abdominal pain associated with a sunken immobile hemithorax with chronic pleural effusion were diagnostic features of malignant pleural mesotheliomas.

Patients who were followed up until the final stage complained of painful swellings in the right hypochondrial region. This condition can be explained either by secondaries in the liver or peritoneum or downward movement of the diaphragm by tumoural masses or by massive effusion.

Tûmoural implantation of the chest wall after thoracentesis thoracoscopy or thoracotomy was very common. In one patient we detected 3 tumoural implantations on 3 different aspiration sites.

We did not encounter any attact of hypoglycaemia.

Laboratory Findings: The pleural fluid was found to be mostly exudative or sero-hemorrhagic. Sedimentation rate in most cases was high. Anemia was common in the late stage. There was no difference between asbestos related mesothelioma and zeolite induced mesothelioma with regard to laboratory findings.

Radiological Findins: We re-evaluated the chest x-rays of 66 patients with mesothelioma. The abnormalities are shown below:

Abnormalities	No.	%
Pleural Effusion	32	48.8
Pleural Thickening	12	13.6
Peripheral Pleural Nodules	9	18.1
Pleural Lesions with CPP	8	12.2
Bone Lesions with Pleural Disease	3	4.5
Hydro-pneumothorax	2	3.0

Method of Diagnosis: All the cases from Tuzkoy (27 cases) had tissue diagnosis, either with Abram's needle biopsy, thoracoscopy or thoracotomy. Twenty-three out of 62 cases from Karain were diagnosed with retrospective studies. The method of diagnosis in the remaining 39 cases were: Pleural needle biopsy, clinical and radiological findings with cytology; thoracoscopy, thoracotomy and postmortem, 15, 11, 8, 4, 1 respectively.

Clinical Course and Prognosis: The average life expectancy in patients was 1.5-2 years.

Malignant pleural mesothelioma was diagnosed in a middle aged patient in Sweden. He underwent pleurectomy, and after the operation, he remained well. However an isolated metastasis in the thoracic wall was found after 2 years. This was removed surgically and radiotherapy combined with chemotherapy was subsequently given.

Another patient from Karain had lobectomy and partial pleurectomy done in West Germany in 1974. After the operation he remained well until 1979 when massive pleural effusion with tumoural infiltration of chest wall developed and he died. There was another patient with a similar clinical course.

A middle-aged female patient sought medical advice for right sided chest pain. Her initial clinical and radiological examinations were normal. However pleural effusion was detected after two weeks on the same side, and pleural needle biopsy revealed malignant mesothelioma with calcified plaques.

GENERAL DISCUSSION

Malignant pleural mesothelioma is a rare tumour and the incidence is estimated to be 1-2 per million person-years in the general population (17).

The results of our previous studies confirmed that there is an extremely high rate of malignant mesothelial tumours in Karain, Tuzköy and Sarıhıdır villages in Cappadocia region (1, 2, 4-10). We collected 94 cases of malignant mesothelioma from these villages. The annual incidence of 216/100,000 cases of malignant pleural mesothelioma in Tuzkoy is at least 942 times higher than expected for this community.

Epidemiological and experimental studies have provided definite evidence that some asbestos fibres induce malignant pleural mesothelioma in exposed populations. However comparing the rate with the asbestos villages, there must be more potent carcinogenic agents in the areas we studied.

Many scientists from different parts of the world have visited and published their findings (11, 13, 15, 25). All of them agreed that the high occurence of pleural tumours cannot be explained by asbestos exposure alone.

As the villages are built upon and into a volcanic area and no other cause of malignant mesothelioma has so far been discovered, it has been suggested that exposure to a naturally occuring fibre could be the cause of the very high incidence of malignant pleural mesothelioma in this Turkish population. Mumpton (19) stated that "Special attention must also be paid to the long-range pathological effects of zeolites in animals, especially of needle-shaped erionite and ultra-thin fibres of mordenite". In fact Pooley (23) identified for the first time erionite and chabazite fibres in samples of rocks and dust from Tuzköy and Karain.

Epidemiological studies have also shown that there was a high incidence of peritoneal mesothelioma and other malignant diseases in the affected villages (1, 2, 9). On the other hand, the prevalence of calcified pleural plaques, chronic pleural thickening and lung fibrosis was high in the zeolite villages, as compared to the control populations (1, 4).

Zeolite minerals are found as the major content in numerous sedimentary volcanic tuffs in Cappadocia region (3, 20, 25). Locally the tuffs have been altered to form a variety of zeolite minerals. The tuff is easily cut into shape and is extensively quarried for building construction.

Karain, Tuzköy and Sarıhıdır were the only villages which had been built upon and into erionite rich zeolite rocks. In the houses where the walls were made from erionite rich zeolite rocks, exposure to the erionite fibres was always possible..

Rom et al. (26) observed fibrosis of the lung and pleura in residents of regions in which fibrous erionite deposits occur. A 52-year-old road construction worker from a zeolite area in Nevada, USA, was found to have extensive pleural and parenchymal fibrosis and small pleural effusion. The patient had no history of asbestos exposure. Numerous particles and fibres chemically consistent with erionite were identified in his lung tissue by electron microscopy. However, chest radiographs (275) of patients over the age of 25 years in 1968 and 1975 and over the age of 50 years in the first eight months of 1980 from a local community hospital were reviewed; the frequency of pleural changes was not considered by the authors to be excessive for a hospital population (26).

McDonald and McDonald did a case-control study of 66% fatal cases of mesothelioma in Canada (1960-1975) and the USA (1972). Seventen cases and 12 controls had lived for 20-40 years before death within 20 miles of zeolite deposits, reportedly of natural zeolites in western USA. A paired analysis gave a relative risk of 1.60 after adjusting for occupational exposure to asbestos.

Environmental studies showed the presence of zeolite fibres in the villages affected by the disease. The measurements of the airborne levels, consistently indicated higher levels in the affected villages when compared to the control ones (8, 10). This is confirmed by the results of sheep lungs analysis where the presence of zeolite fibres broadly correlates with the geographical distribution of the disease (10).

Unfortunately, no systematic investigation of the human lung contents has been possible due to the local situation. However, the data from 10 cases (7 malignant pleural mesothelioma; and one each of chronic fibrosing pleuritis, diffuse lung fibrosis and hamartoma) from Karain, Tuzköy and Sarıhıdır clearly indicates an accumulation of erionite fibres in the lungs both in absolute terms and in relation to other types of fibres (9 - 11, 28).

The accumulation of zeolite fibres in the lungs is consistent with the findings by Sebastien et al. (28). During a survey in four villages in the same area, the authors found a significant correlation between the presence of ferruginous bodies, previously identified by the same authors as "Zeolite Bodies" in the sputum and the residence of those in the affected villages (29). The authors conclude that "... people (in the affected villages) have continuously inhaled zeolite fibres, accumulating with age to reach a high concentration in their lungs." The chemical structure of the zeolite fibres analysed correspond to that of erionite, which is thus the major component of the exposure to zeolite fibres in the population under study.

The effects of erionite exposure studied in animals showed a high carcinogenic potential both by inhalation and with other modes of application (14, 16, 24, 30-33).

Özesmi and co-workers (21) injected intraperitoneally a ground sample of rock from Karain in mice and observed a number of mesotheliomas and lymphomas.

The carcinogenic power of erionite appears stronger than any other mineral fibre so far studied and it has been suggested that additional properties of erionite might enhance the carcinogenic potency of this fibre (32).

These data are consistent with results of the *in vitro* experiments by Poole and colleagues (22) who demonstrated the genotoxic activity of fibrous erionite. The authors point to the fact that erionite appears to be more active than crocidolite and suggest a qualitative different activity in inducing free radial chain reactions capable of causing cellular and subcellular damage.

Erionite fibres tend to split longitudinally but do not show size characteristics significantly different from other carcinogenic fibres like crocidolite which rather presents a higher proportion of fine fibres. Further experimental research is required to explain the carcinogenic properties of erionite which appears to be the most powerful fibrous carcinogen so far studied.

The results of our latest collaborative study (10) provide evidence that high incidence of mesothelioma and other malignant diseases correlates with the exposure to zeolite fibres. Quantitative and qualitative aspects of the exposure have not been fully ascertained. The data appear to be consistent with a lifetime exposure to a carcinogenic fibre which tends to accumulate in the lungs (27).

Some exposure to other asbestos fibres such as tremolite and chrysotile have been documented in zeolite villages (11, 25). Their role in increasing the cancer risk in the exposed population cannot be excluded, but does not appear to correlate with the distribution of the disease.

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CONCLUSION ON ERIONITE - RELATED DISEASES

Environmental and epidemiological studies have been carried out in Karain, Tuzköy and Sarıhıdır and confirmed that naturally occuring fibrous zeolite (Erionite) is the cause of the high incidence of malignant mesotheliomas, other malignancies, lung fibrosis and benign pleural diseases in the area.

The effects of erionite exposure have been studied both *in vivo* and *in vitro*, and showed that erionite appears to be the most powerful fibrous mineral carcinogen so far studied.

It has been suggested that apart from its similarities with crocidolite, additional properties of erionite might enchance its potency.

From the epidemiological and case-control studies, one can easily understand that fibrous zeolite can induce disorders that are mentioned in Table 48.

TABLE 48: Erionite-Related Diseases

I. Neoplastic diseases
   1. Mesotheliomas
      Pleural
      Peritoneal
   2. Bronchial carcinomas
   3. Extra-pulmonary carcinomas

II. Pneumoconiosis "Zeolitosis"

III. Pleural reactions
   1. Pleural effusions
   2. Pleural thickening
   3. Pleural plagues
      Hyalinized
      Calcified

SUGGESTED PREVENTIVE MEASURES FOR ZEOLITE VILLAGES

The goverment should help for the re-settlement of Karain and Tuzkoy villagers in a new area because of serious health hazards of fibrous zeolite.

We are aware that there are some villagers who do not want to move. They should be educated though public conferences, radio broad casts and television programs on the health hazards of erionite.

In order to prevent air pollution with fibrous zeolite, sources of erionite such as quarries and volcanic tuffs must be covered with non-fibrous soil and grass planted over them.

At least once a year, clinical and radiological screening should be carried out amongst the inhabitants of the three villages by trained physicians who have expertise in zeolite related diseases.

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A house in a village which is plastered with asbestos mixed white soil.

Karain Village. Black dwelling caves made by man inside fairy chimneys just behind the village gives the name of village.

Fiyatı : 4000 TL.