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Understanding Human Illness and Death Following Exposure to Particulate Matter Air Pollution

Erin M. Tranfield and David C. Walker
The James Hogg Research Centre, Providence Heart and Lung Institute, St. Paul's Hospital, University of British Columbia, Vancouver, Canada

1. Introduction

The World Health Organization (WHO) estimates that more than two million deaths occur each year as a consequence of air pollution exposure (Mackay et al., 2004). This estimate, which some scientists consider conservative, is based on hundreds of scientific studies showing an association between exposure to air pollution and heart as well as lung related illness and death. However, scientists do not understand the sequence of events in the human body that link air pollution exposure to illness and death. Understanding these events and their order is a major focus of ongoing medical research.

The aims of this chapter are to first introduce the reader to air pollution and then to briefly present the current scientific understanding of the biological events that link particulate matter air pollution exposure to illness and death. The chapter concludes with suggestions for future actions to reduce the health consequence of air pollution exposure. This chapter does not consider the effects of indoor air pollutants such as tobacco smoke, or smoke from cooking fires because these topics are considered elsewhere in this book.

Air pollution is a complicated mixture of airborne particulates combined with gases, mist and fog. Its composition is highly variable with differences observed between rural locations and cities, between individual cities, and even between regions within cities. The gases in air pollution such as ozone, carbon monoxide, sulphur dioxide and nitrogen dioxide are considered pollutants at high levels because they have a moderate association with human illness (morbidity) and death (mortality) (Lipfert et al., 1995; Morris et al., 1995; Sheppard et al., 1999; Wichmann et al., 1989). When small enough to enter the deep regions of the body, particles in air pollution have been shown to have a strong association with human morbidity and mortality, particularly with heart (cardiovascular) and lung (pulmonary) morbidity and mortality (Dockery et al., 1993; Hong et al., 1999; Lin et al., 2005; Pope, 1989; Samet et al., 2000; Stieb et al., 2002; Wichmann et al., 1989). These small particles are called particulate matter.

1.1 Particulate matter

> **PM_{10}** – Atmospheric particles with an aerodynamic diameter smaller than 0.00001 meter or 10 micrometer

The WHO defines particulate matter (PM) as a stable atmospheric suspension of solid and liquid particles with variable composition, origin and an aerodynamic diameter ranging from ~0.000000002 to ~0.0001 meter (m). Particles with an aerodynamic diameter smaller than 0.00001 m, or 10 micrometer (μm), are strongly associated with human morbidity and mortality and are commonly referred to as PM_{10}.

1.1.1 Particle size

Particle size plays a central role in determining the biological consequences of PM exposure (Finlayson-Pitts et al., 2000; Oberdorster, 2001). Particle size has been shown to determine: 1. the location of particle deposition in the airway and lungs, 2. the amount of surface area that can contact tissues, and 3. the rate of particle clearance from the lungs (Kendall et al., 2002; Oberdorster et al., 1994; Sioutas et al., 2005; West et al., 2003).

Particles larger than 10 μm in diameter have such high inertia that they cannot turn the tight corners of the airway. As a result these particles run into the mucous covered walls of the nose and upper airway where they become trapped. The mucous holds these particles until the particles are cleared through mucociliary clearance. Due to the location of deposition in the upper airway, particles larger than 10 μm in diameter are not associated with human illness. Mucociliary clearance is a cleaning system in the airway made of small hairs called cilia. Cilia transport mucous and any debris the mucous has trapped to the upper airway for clearance through the nose or swallowing into the stomach.

Particles smaller than 10 μm in diameter have a small enough inertia that the particles can navigate the upper airway and be inhaled deep into the lungs. Particle deposition on the alveolar surface, which is where gas exchange occurs in the lungs, is linked to pulmonary and cardiovascular morbidity and mortality (Dockery et al., 1993; Seaton et al., 1995). Analysis of PM_{10} has recently revealed three fractions of PM_{10} with distinct regions of deposition in the lungs. These three fractions are the coarse fraction, the fine fraction and the ultrafine fraction. Each fraction has different formation processes, composition, atmospheric lifetimes and biological consequences (Sioutas et al., 2005).

The coarse fraction is composed of particles between 10 and 2.5 μm in aerodynamic diameter that are produced by mechanical processes such as wind erosion. These larger particulates are affected by gravitational settling and typically settle out of the lower atmosphere within hours of formation (Hinds, 1999; Sioutas et al., 2005). The coarse fraction is thought to deposit in the upper airway, and to penetrate only as deep as the pharynx and occasionally into the trachea. Similar to the greater-than-10 μm fraction, particles deposited in these areas are cleared from the body through the nose or by coughing and swallowing. The particles that enter deep into the pulmonary system are carried up the trachea by the mucociliary escalator and swallowed into the stomach.

The fine fraction is composed of particles between 2.5 and 0.1 μm in size and is called $PM_{2.5}$. These particles account for the greatest mass of airborne particulates and are generally formed through human activities. Fine particle formation typically occurs when gas molecules condense together to form particles through heterogeneous and homogeneous nucleation, as well as condensation onto already existing atmospheric particles (Finlayson-Pitts et al., 2000; Hinds, 1999; Sioutas et al., 2005). The small size of this fraction of particles makes them less susceptible to gravitational settling resulting in atmospheric lifetimes in the order of days, and the ability to be transported long distances by wind currents. The fine particles are inhaled into the conducting airways of the lungs. The mucociliary escalator also clears particles deposited in these areas. Some particles travel beyond the conducting airways into the alveoli where they become trapped in the fluid layer of the alveolar wall. In the alveoli, a population of resident white blood cells, called alveolar macrophages, patrols the alveolar surfaces immediately below the layer of fluid. Particles deposited on the alveolar wall are taken up by these alveolar macrophages. The macrophages are then transported out of the lungs by the mucociliary escalator (Dockery et al., 1994) or taken to the pulmonary lymph nodes (Harmsen et al., 1985). A small population of free particles that are not taken up by alveolar macrophages may move into the lung tissue, and then be taken into the lymphatic vessels for processing in the pulmonary lymph nodes (Dockery et al., 1994). Depending on their solubility, particles may remain in the pulmonary lymph nodes from several days to thousands of days (Brain et al., 1994).

Coarse - PM_{10}: Deposited in the upper airway; until recently associated with human illness.

Fine - $PM_{2.5}$: Deposited deep into the lungs, some deposition on the alveolar surface; associated with human illness**.**

Ultrafine - $PM_{0.1}$: Deposited on the alveolar surface, may enter the blood stream; associated with human illness.

The ultrafine fraction is composed of particles that are smaller than 0.1 μm in aerodynamic diameter ($PM_{0.1}$). These particles have traditionally been considered the fresh emissions in pollution that have yet to undergo condensation or modification processes. The composition of fine particles is varied, characteristically composed of ammonium, carbon, nitrate and sulphate as well as trace metals formed in the combustion processes (Sioutas et al., 2005). This fraction of the smallest particles accounts for the greatest number of atmospheric particles with the largest surface area-to-mass ratio. These particles are primarily deposited on the alveolar surface (Naga et al., 2005; Wang et al., 2002; West et al., 2003). Smaller particles are thought to move into the pulmonary circulation as evidenced by their accumulation in the lymph nodes, spleen, heart, liver and even the bladder and brain (Brain et al., 1994; Harmsen et al., 1985; Nemmar et al., 2002; Oberdorster et al., 2000; Oberdorster et al., 2004; Peters et al., 2006; Semmler et al., 2004).

The large surface-area-to-volume/mass ratios of fine and ultrafine particles may account for their negative effect on human health. Evidence suggests that the larger the surface area the greater the impact of the particle. Smaller particles are known to have the greatest surface

area relative to their volume or mass (Oberdorster et al., 1994) as well as the greatest efficiency at penetrating deep into the lungs (Sioutas et al., 2005).

Collecting air pollution particles without modifying them has been a problem for scientists. Furthermore, once the particles are collected it has been difficult to separate PM into the above mentioned size fractions. Because of this, most research is done using material fractioned only by the upper size limit. As such, PM_{10} used in research is composed of PM_{10} + $PM_{2.5}$ + $PM_{0.1}$, and $PM_{2.5}$ is composed of $PM_{2.5}$ + $PM_{0.1}$. In the rest of this book chapter, the use of PM_X represents particulate matter *up to* X micrometers in aerodynamic diameter.

1.1.2 Particle formation

In general, two main processes form PM. The first process is the condensation of gases in the lower atmosphere. The second process is direct introduction of PM through mechanical means such as wind blowing over exposed soil or human activities that stir up dust particulates such as farming and construction activities (Figure 1). Industry and combustion also directly introduce particulates into the atmosphere. Source variability and formation processes affect size distribution and particle composition of PM. Particles larger than 10 µm in diameter are primarily generated by wind blowing over soil whereas human activities, particularly the combustion of fossil fuels, are by far the greatest generators of PM_{10}.

1.2 Regulation of particulate matter

In 2005, the World Health Organization updated the daily and annual mean guidelines of acceptable air pollution. These standards are still in effect and advise that within a 24-hour period, the mean level of $PM_{2.5}$ should not exceed 25 µg/m^3 and the mean level of PM_{10} should not exceed 50 µg/m^3. Furthermore, over the course of a year, the mean level of $PM_{2.5}$ should not exceed 10 µg/m^3 and the mean level of PM_{10} should not exceed 20 µg/m^3. Mean standards per 24-hours are higher than mean standards per year to allow for infrequent air pollution events caused by non-controllable factors such as wild fires or weather pattern changes. Data gathered prior to 2000 suggest that most large American cities would not have met these updated standards (Peng et al., 2005); however, PM_{10} levels are gradually decreasing with the implementation of pollution-minimization measures.

Fig. 1. Particulate matter is introduced into the atmosphere through many human activities including vehicle emissions (panel a), industrial towns in developing countries like China (panel b) and general farming practices (panel c). Image credits E Tranfield.

1.3 Worldwide air pollution standards

The guidelines set by the World Health Organization in 2005 are not followed by all countries (Table 1). Current efforts are being made by most developed countries to reduce the levels of air pollution and achieve these guidelines. Although a lot of progress has been made to reduce air pollution production in general, and PM production specifically, further reductions are required. Moreover, in rapidly developing countries like China, and India, which are currently some of the greatest sources of pollution, only minimal efforts are being made to reduce the generation of pollution.

1.4 The global nature of air pollution

Fine particulates are small enough to remain suspended in the air for long periods of time and to be transported by prevailing winds over long distances. This means that pollutant production can have a global impact and there is evidence that pollution from China has reached the west coast of North America. Efforts by individual countries will have local effects on air quality but to generate long-term global health benefits air pollution will need to be prevented, regulated and monitored on a global scale.

Country	Pollutant	Targeted limits	References
Australia	PM_{10}	24 hr maximum: 50 μg/m^3	Australian Government, 2009
	$PM_{2.5}$	24 hr maximum: 25 μg/m^3; Annual maximum: 8 μg/m^3	
Canada	$PM_{2.5}$	24 hr maximum: 30 μg/m^3	Canadian Council of Ministers of the Environment, 2000
European Union	PM_{10}	24 hr maximum: 50 μg/m^3; Annual maximum: 40 μg/m^3	European Commission Environment, 2011
	$PM_{2.5}$	Annual maximum: 25 μg/m^3	
United States of America	PM_{10}	24 hr maximum: 150 μg/m^3	United States Environmental Protection Agency, 2011
	$PM_{2.5}$	24 hr maximum: 35 μg/m^3; Annual maximum: 15 μg/m^3	
World Health Organization Recommendations	**PM_{10}**	**24 hr maximum: 50 μg/m^3; Annual maximum: 20 μg/m^3**	**World Health Organization, 2005**
	$PM_{2.5}$	**24 hr maximum: 25 μg/m^3; Annual maximum: 10 μg/m^3**	

Table 1. Examples of ambient particulate matter guidelines.

2. Understanding particulate matter induced human morbidity and mortality

Efforts to understand the sequence of events and the mechanisms through which air pollution affects human health have relied on two complimentary approaches.

The first approach is to use epidemiological investigations to study an illness in a large group of people and determine trends and patterns between the illness and potential causes of this illness. Epidemiological investigations are an effective public-health approach used to rapidly narrow down the potential causes of an illness but with little understanding of the underlying biochemical processes taking place.

> *Epidemiological* investigations and *medical* research are two complementary approaches that are used to understand how air pollution affects human health.

The second approach is to use medical research to understand the biochemical processes that are occurring within each person at the organ, tissue and even protein level. Medical research is more specific than epidemiological investigations in determining the cause of a medical event through a detailed understanding of the sequence of processes happening in the body. However, since medical research is very time consuming, epidemiological investigations help to rule out potential causes of illness, thus efficiently reducing the scope for medical investigations.

Scientists have been using a combination of these two approaches to understand how exposure to air pollution, particularly PM, is impacting processes within the body and leading to cardiovascular and pulmonary morbidity and mortality.

2.1 Epidemiological investigations

2.1.1 Human awareness of the impact of air quality on health

The first known environmental legislation was documented in Israel about 2000 years ago. Practitioners of the Jewish religion suspected a relationship between human illness and the foul odors of tanneries as well as the airborne waste products from threshing floors. Laws stipulated that industries should be located down-wind of cities and towns to minimize the exposure of citizens to airborne pollutants (Mamane, 1987).

Over 1600 years later, in 1661, John Evelyn wrote to the King of England regarding the soot in the air over London. He attributed chronic coughs and pulmonary mortalities to the air quality and he put forward recommendations to move industry outside the city to reduce air pollution (Evelyn, 1965). The suggestions of John Evelyn were ignored and air pollution levels continued to rise, pushed upwards by the 18th century industrial revolution.

In 1930, 63 people died during an air pollution episode in the Belgian Meuse Valley (Nemery et al., 2001). In 1948, 20 people died, several animals died and 43% of the 14,000 inhabitants became ill after a weather inversion in the highly industrialized town of Donora, Pennsylvania, trapped coal smoke, sulphur dioxide, soluble sulphates, and fluorides over the city (Schrenk et al., 1949). Yet, the event cited as the major turning point in air pollution awareness and public policy did not occur until 1952. In December of that year, London, England, suffered an absence of wind and a temperature inversion resulting in a very dense fog over the Greater London area. PM produced by the burning of coal was trapped within the fog, leading to a rapid and extreme rise in air pollution followed closely by a rapid and

extreme rise in mortality rates. During the infamous four day pollution event in excess of 4000 deaths above typical levels occurred (Logan, 1953). In response to the startling number of air pollution related deaths, the British Parliament passed a Clean Air Act in 1956 to reduce emissions of airborne pollutants.

Since 1952 the search for the causative agent of air pollution related mortality has been pursued and gradually narrowed down to PM_{10}. In 1979 an epidemiological investigation suggested airborne particulates were responsible for some of the observed cardiopulmonary health effects (Holland et al., 1979). Nonetheless, it was not until a standardized definition of PM was introduced in 1987 by the United States Environmental Protection Agency, and statistical analysis was used to remove major confounding factors including smoking, socioeconomic status, and body-mass index that the first robust positive association between mortality and PM air pollution was established in 1993 (Dockery et al., 1993).

2.1.2 Epidemiological evidence

Today epidemiological studies present strong evidence that exposure to ambient PM_{10} contributes to cardiopulmonary morbidity and mortality (Dockery et al., 1993; Pope, 1989; Samet et al., 2000). Cardiovascular diseases are much more common in the world than pulmonary diseases and so there are more cardiovascular events following PM_{10} exposure than there are pulmonary events. Specifically, the number of heart attacks, strokes, aggravations of heart failure, cardiac arrhythmias and sudden deaths increase within hours of exposure to elevated levels of PM_{10} (Hong et al., 2002; Peters et al., 2000; Peters et al., 2004; Pope et al., 2004; Schwartz, 1994).

2.1.3 Limitations of epidemiological investigations

Epidemiological investigations can establish strong patterns and associations between an event and a cause, in this case between cardiovascular morbidity and mortality and ambient PM_{10} exposure. Epidemiological investigations can suggest organs, and tissues of interest that should be studied in detail by medical research but epidemiological investigations cannot explain the detailed biochemical processes that are occurring in the body as a result of air pollution exposure – for that scientists rely on medical research.

2.2 Medical research

2.2.1 Pulmonary health concerns

Air pollution predominately enters the body during breathing; therefore, investigating the effects of PM inhalation on the lungs was an initial focus of many research groups interested in air pollution. There is an extensive amount of literature in this field and the authors refer readers to the following reviews for more information on this topic (Ko et al., 2009; Laumbach, 2010; Ling et al., 2009; Liu et al., 2008).

To briefly summarize the progress made in the field, it has been found that short-term exposure to high levels of PM_{10} and ozone lead to altered pulmonary function in children and in adults (Kelly et al., 2011; Sheppard et al., 1999). The consequences of long-term exposure to high levels of PM_{10} include worsening of chronic obstructive pulmonary disease

(COPD)(Liu et al., 2008), and the development of chronic bronchitis and potentially lung cancer, although the later is still under debate (Gamble, 2010). Additionally, research has shown compromised lung development in children (Gauderman et al., 2007) and an increased risk of developing asthma and allergies (Kelly et al., 2011). Populations at risk of serious pulmonary consequences when exposed to elevated levels of pollutants are the elderly (Schwartz, 1995) or individuals with existing conditions such as pneumonia (Knox, 2008), asthma or COPD (Pope et al., 1995).

As the epidemiological evidence became stronger that exposure to PM also had an effect on the cardiovascular system, research groups began to study the underlying processes that might be responsible for cardiovascular related morbidity and mortality.

2.2.2 Cardiovascular health concerns

Introduction to cardiovascular disease and terminology

Before we look in detail at some of the medical research on this topic, it is important to understand the basic architecture of a healthy blood vessel. A blood vessel has three layers: the adventitia, the media and the endothelium. The media is the middle layer and the muscle layer of the blood vessel. It is populated with many smooth muscle cells. For arteries the media is quite thick, but for veins the media is rather thin. The innermost layer of the blood vessel is the endothelium, which is made of a single layer of endothelial cells that are anchored to a thin layer of structural proteins called the extracellular matrix (ECM). The endothelium is the barrier between the blood in the blood vessel and the cells and proteins of the blood vessel. Just like the liner of a swimming pool, if small holes appear in the endothelium it will cause problems. Blood clots, medically called a thrombosis, will form to prevent leakage of the blood vessel. A large thrombosis can block blood flow where it forms, or it can break off and travel in the blood until it gets stuck fully blocking a small blood vessel. A blocked blood vessel in the heart results in a heart attack (medically called a myocardial infarction), a blocked blood vessel in the brain results in a stroke. Events such as these are very rare when the blood vessel wall is healthy, but these events increase when the blood vessel is diseased such as when a person has atherosclerosis. Atherosclerosis is a disease of the medium and large blood vessels, typically characterized by fatty deposits under the endothelium of the vessel wall. A stable atherosclerotic plaque has lipid accumulation at the core, and a "cap" of smooth muscle cells and ECM (Virmani et al., 2002) (Figure 2a). This cap is important in keeping the lipid away from the blood and providing a stable anchoring surface for the endothelial cells. Myocardial infarctions and strokes typically occur when an area of an atherosclerotic plaque does not have a dense cap, and becomes unstable. The plaque may rip, crack or a region may break off. In all cases the contents of the plaque will come in contact with blood and a thrombosis will form blocking blood flow, either at the plaque or further downstream in the blood vessel. Individuals at risk of myocardial infarctions or strokes have large fatty atherosclerotic plaques that do not have a stable, dense cap (Virmani et al., 2002).

White blood cells play an important role in atherosclerotic plaques. There are several different kinds of white blood cells, but the most important in atherosclerotic plaque development is the monocyte / macrophage. These cells are important cells in the immune

system. In their young form they circulate in the blood and are called monocytes. In response to a local immune signal indicated by signaling proteins called cytokines, monocytes can move out of the blood into the tissues and mature into immune cells called macrophages. Macrophages attempt to clear the foreign object, or infectious agent from the body. In the development of atherosclerotic plaques, monocytes easily enter the leaky blood vessel wall, become macrophages and take up the lipid that is accumulating in the wall. Fat filled macrophages are called macrophage-derived foam cells.

Research has also shown that cytokines are produced in response to particles deposited in the lungs. Monocytes move into the lungs, where they become alveolar macrophages. Alveolar macrophages take up the particles in an effort to clear the particles from the body.

The three mechanisms to explain how air pollution affects the heart

The epidemiological link between PM_{10} exposure and cardiovascular related morbidity and mortality is convincing; however, the underlying biological mechanism(s) remain(s) unclear. There are three primary mechanisms by which PM air pollution may bring about cardiovascular events. These are the inflammatory mechanism, the dysfunction of the autonomic nervous system mechanism and the cardiac malfunction mechanism.

> The three mechanisms that attempt to explain how air pollution affects the heart are the *inflammatory* mechanism, the *dysfunction of the autonomic nervous system* mechanism and the *cardiac malfunction* mechanism.

The inflammatory mechanism was originally proposed by Seaton and colleagues (Seaton et al., 1995). They hypothesized that exposure to air pollution irritates the lungs, particularly in patients with existing pulmonary conditions such as asthma and chronic obstructive pulmonary disease. This results in the release of cytokines in the lungs. The cytokines enter into the blood and begin a low level immune response (also called an inflammatory response) through the body. Seaton and colleagues proposed that the resulting low-grade systemic inflammatory response was involved in the observed cardiovascular events following air pollution exposure. In 1999, Seaton and colleagues showed a correlation between a decrease in the number of circulating red blood cells and PM_{10} exposure (Seaton et al., 1999). Subsequent medical studies have shown that PM_{10} exposure results in platelet activation, (Nemmar et al., 2003) and early release of white blood cells, specifically neutrophils (Mukae et al., 2000) and monocytes (Goto et al., 2004), into the circulation. Furthermore, epidemiological studies on human populations have shown an increase in the number of circulating white blood cells (Tan et al., 2000), and increased clotting and inflammation indicators in the blood (Gilmour et al., 2005). These are all observations that support the theory put forward by Seaton and colleagues in 1995 that PM_{10} exposure leads to low-grade, body-wide inflammation.

The second mechanism centers on the dysfunction of the autonomic nervous system resulting in changes in heart rate, heart rhythm and blood pressure. Epidemiological studies on human populations provide evidence that PM_{10} exposure results in a decrease in heart rate variability (Pope et al., 1999), and an increase in heart rate (Pope et al., 1999), cardiac

arrhythmias (Peters et al., 2000), systolic blood pressure, (Ibald-Mulli et al., 2001) plasma viscosity (Peters et al., 1997), and arterial vasoconstriction (Brook et al., 2002). In animal studies, exposure to PM_{10} affects heart rate and blood pressure (Cheng et al., 2003), and increases arrhythmias (Watkinson et al., 2001), and fibrinogen levels (Ulrich et al., 2002). Together this data suggests that some component of PM triggers dysfunction of the autonomic nervous system, yet what that component is and how it triggers dysfunction remains unknown.

The final proposed mechanism involves particulate induced cardiac malfunction caused by particulates in the blood stream (Nemmar et al., 2002; Oberdorster et al., 2000; Oberdorster et al., 2004) leading to local damage to the heart muscle (Park et al., 2005) as well as the liver (Oberdorster et al., 2000) and the blood vessels (Schulz et al., 2005). Of the three proposed mechanisms, the cardiac malfunction mechanism has the least research and supporting data.

Understanding what processes are involved, how these processes are initiated and what the short- and long-term consequences of PM_{10} and $PM_{2.5}$ exposure are is the focus of ongoing research. The big questions can be grossly simplified to this: how does the air we breathe cause changes in our cardiovascular system and in extreme cases lead to the rupture of atherosclerotic plaques?

Medical research investigating how exposure to particulate matter affects the cardiovascular system

Studies from the Davis Heart & Lung Research Institute at Ohio State University reported increased lipid deposits and macrophage invasion into the wall of atherosclerotic plaques in an atherosclerotic mouse model, (ApoE -/- mouse) following long-term exposure to low concentrations of $PM_{2.5}$. In these same animals they reported reduced responsiveness of the blood vessel wall, and increased area of atherosclerotic plaques (Sun et al., 2005). They also found increased tissue factor expression, which is another indicator of inflammation, following exposure to particulate matter (Sun et al., 2008). Together these observations suggest a worsening of inflammation and atherosclerosis in mice after exposure to $PM_{2.5}$.

Work done by our laboratory at the James Hogg Research Center showed structural changes in atherosclerotic plaques from Watanabe Heritable Hyperlipidemic (WHHL) rabbits exposed to PM_{10} (Suwa et al., 2002; Tranfield et al., 2010; Yatera et al., 2008) and from ApoE -/- mice exposed to diesel exhaust (Bai et al., 2011). The observed changes were consistent with atherosclerotic plaques vulnerable to rupture.

Light microscopic studies reported a trend towards larger atherosclerotic plaques, increased infiltration of inflammatory cells, recruitment of monocytes and increased amounts of lipid accumulation in the plaques from rabbits exposed to PM_{10}. These studies document greater numbers of atherosclerotic plaques classified as advanced vulnerable plaques following exposure of the rabbits to PM_{10} (Suwa et al., 2002; Yatera et al., 2008).

Our electron microscopy studies showed three critical findings: 1. an accumulation of macrophage-derived foam cells immediately below the endothelium of atherosclerotic plaque cores, 2. the separation of the endothelium from a previously undescribed reticulum of dense extracellular matrix (ECM) that serves as the supporting layer of atherosclerotic plaques, and 3. evidence of degradation or fragmentation of the dense ECM in regions of macrophage-derived foam cell accumulation (Tranfield et al., 2010). As a consequence of

fragmentation of the ECM, there was increased direct contact between macrophage-derived foam cells and the endothelial cells. Furthermore, increased macrophage-derived foam cell migration was observed over the core regions of atherosclerotic plaques from PM_{10} exposed rabbits. The evidence suggests that the cells were emigrating out of the atherosclerotic plaques and into the lumen of the aorta (Tranfield et al., 2010).

In the atherosclerotic plaques of the rabbits exposed to PM_{10}, we observed an absence of the dense ECM under the endothelial cells. Rather, we observed macrophage-derived foam cells (Figure 2b) or fragmented ECM (Figure 2c) under the endothelial cells, neither of which would provide a stable attachment surface for the endothelial cells. Quantification of these observations found that in PM_{10} exposed rabbits, 21.6% of the endothelial cell contacts were with fragmented ECM, whereas only 8.4% of endothelial contacts in control rabbits were in contact with fragmented ECM ($p < 0.0001$). The number of endothelial cell contacts with macrophage-derived foam cells was found to be 13.4% in the control rabbits and increased significantly to 38.1% in PM_{10} exposed rabbits ($p = 0.0039$) (Tranfield et al., 2010).

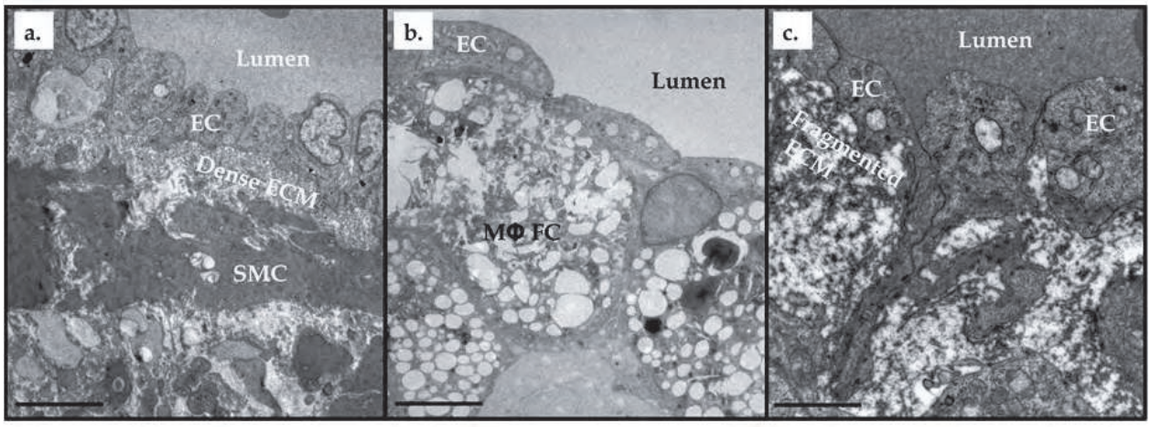

Fig. 2. The wall of an atherosclerotic plaque from a control rabbit contained smooth muscle cells (SMC) and unique dense extracellular matrix (ECM) under the endothelial cells (EC) (panel a). The wall of an atherosclerotic plaque from a rabbit exposed to PM_{10} has large lipid filled macrophage-derived foam cells (MØFC) directly under the endothelial cells (EC) (panel b) or fragmented ECM near areas of MØFC accumulation (panel c). Scale bars: a. 5 µm, b. 5 µm and c. 2 µm. Panel a and b originally published in Tranfield et al., 2010.

To better understand changes in the contact between the dense ECM and the endothelial cells, serial thin section reconstructions were done using transmission electron microscopy (Figure 3). Many contacts between the endothelial cell and the ECM were observed in the reconstructions from the control rabbits. In contrast, the endothelial cell in the reconstructions from the PM_{10} exposed rabbits had a fragmented underlying ECM and few contacts between the ECM and the endothelial cell. These observations suggest decreased stability of the endothelial cell attachments following PM_{10} exposure.

A distinction needs to be made between the core regions of an atherosclerotic plaque and the edges of an atherosclerotic plaque. In Figure 4a the edges of the plaque are outlined with white arrows whereas a white diamond marks the plaque core. Typically more stable atherosclerotic plaques grow from the edges with the center having a fibrous cap. Evidence

of cell migration, lipid accumulation and plaque expansion is expected at the growing edges. As we were interested in structural indicators of instability, we focused our research on the typically-stable plaque cores well away from the active edge regions. Using a combination of transmission electron microscopy and scanning electron microscopy we observed large lipid-filled cells exiting the core regions of the atherosclerotic plaques from PM_{10} exposed rabbits (Figure 4c, d, e and f). This finding was quite unexpected.

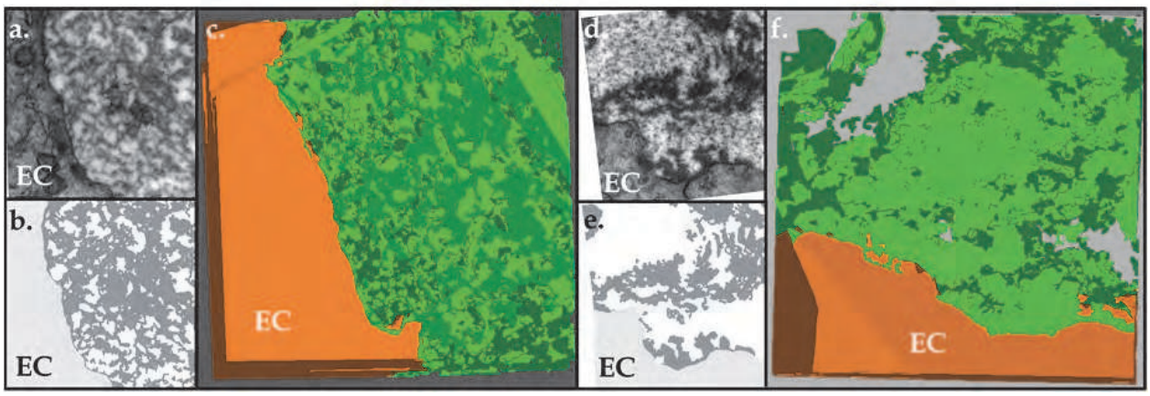

Fig. 3. Three-dimensional reconstruction of the extracellular matrix (ECM, green in c and f) under an endothelial cell (EC, orange in c and f). Panels a-c are from a control rabbit. Panels d-f are from a PM_{10} exposed rabbit. Panels a and d are a single transmission electron micrograph from the series of reconstructed images. Panels b and e are the tracing of the endothelial cell and the dense extracellular matrix shown in panel a and d respectively. Panels c and f are the full reconstruction made of 20 serial tracings from thin sections and show that the contact area between the EC and the ECM is much greater in the control reconstruction than the PM_{10} reconstruction. Methodology and further figures are published in Tranfield et al., 2010.

When all these observations are taken together we believe we have significantly contributed to the understanding of how air pollution may trigger cardiovascular events. An accumulation of macrophage-derived foam cells subtending the endothelium, decreased endothelial contact with a dense, stable reticulum of ECM material and the emigration of large leukocytes from atherosclerotic plaques are indicators of atherosclerotic plaque remodeling following PM_{10} exposure. Taken together with previous work, these findings illustrate mechanisms of remodeling following exposure to PM_{10} that may convert stable atherosclerotic plaques into unstable atherosclerotic plaques. Cardiovascular disease affects millions of people and it appears that PM_{10} exposure may be a considerable contributor to endothelial destabilization and dysfunction potentially being involved in millions of deaths annually. Although PM_{10} exposure is not usually considered an initiating risk factor for atherosclerosis, it appears to be an exacerbating risk factor, pushing existing atherosclerotic plaques to a more vulnerable phenotype.

2.2.3 At-risk groups for cardiovascular complications following PM_{10} exposure

Epidemiological investigations have identified several at-risk groups. Particulate air pollution exposure has been repeatedly linked to adverse events in individuals with a prior

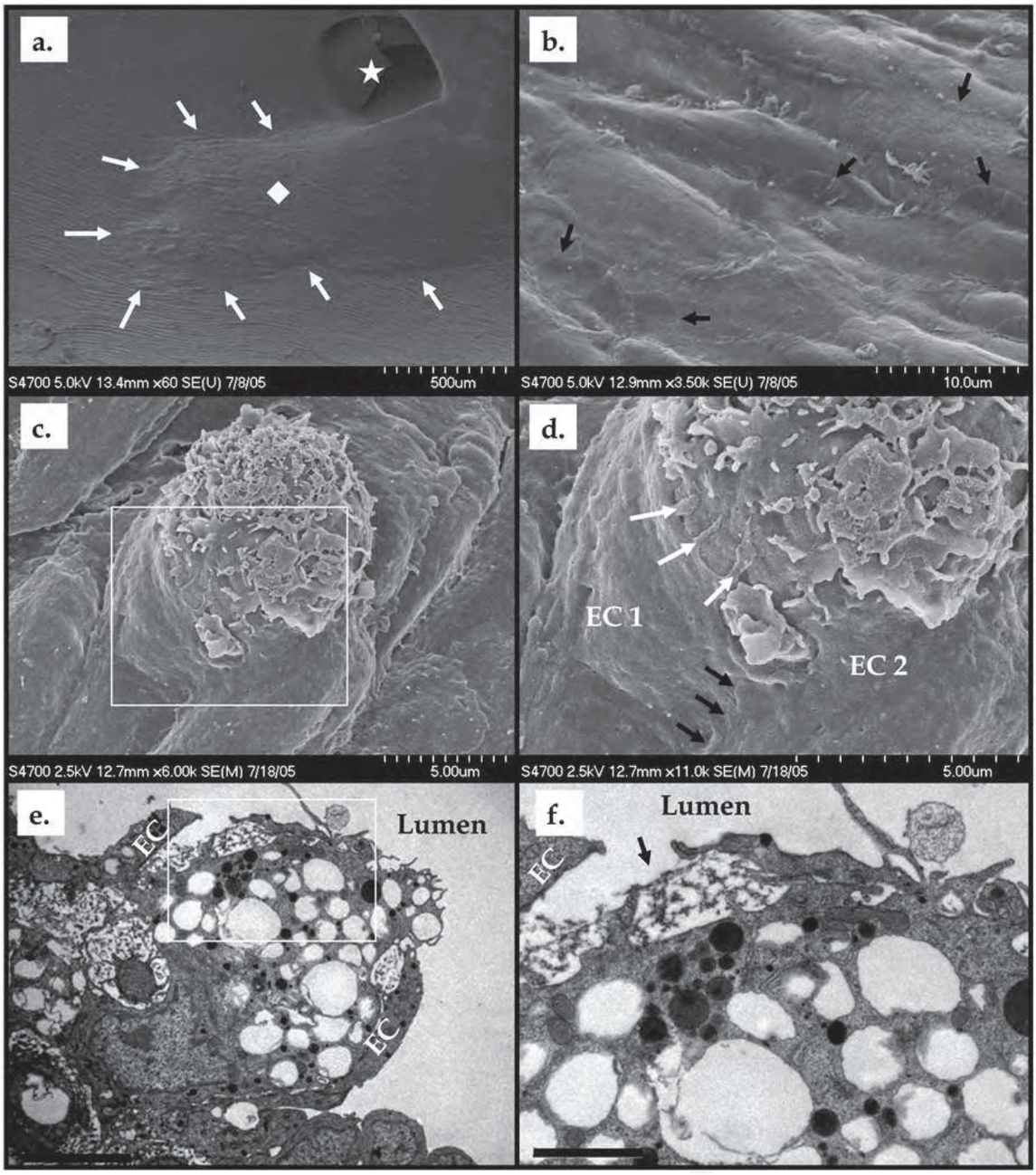

Fig. 4. Electron micrographs of the aorta. Panel a: The core region (◆) of an atherosclerotic plaque (outlined by white arrows) at a branch in the aorta (*). Panel b: Cell borders of healthy endothelium (black arrows). Panels c and d: Cell pushing between two endothelial cells into the blood vessel lumen. The border (black arrows) between the two endothelial cells (EC1 and EC2) and the EC finger-like projections up the side of the migrating cell (white arrows). Panel e and f: Transmission electron micrographs of a macrophage-derived foam cell pushing the endothelial cells aside (EC) as it emerges into the blood vessel lumen. Panel f: Extracellular matrix (arrow) caught above the migrating cell, which would only be possible if the cell is migrating out of the wall. Scale bars: e = 5 μm; f = 2 μm. All micrographs originally published in Tranfield et al., 2010.

myocardial infarction or chronic diabetes, both of which are associated with advanced atherosclerotic disease. Furthermore, exposure to $PM_{2.5}$ had a significant effect in ApoE -/- mice fed high fat chow, whereas a diminished effect was observed in ApoE -/- mice on regular chow diets. Collectively, these observations suggest that PM exposure has a negative impact in combination with high lipid diets, and existing atherosclerosis. Atherosclerotic plaque disruption with thrombus formation is the predominant mechanism leading to unstable angina, myocardial infarctions and sudden death. Therefore, it seems likely that air pollution related morbidity and mortality may also be associated with advanced atherosclerotic disease and plaque disruption.

2.2.4 PM_{10} exposure affects cardiovascular morbidity and mortality: A proposed mechanism

If you will, imagine an individual who is aging, who has at least one or two major risk factors for atherosclerosis and who has been chronically exposed to low levels of air pollution. Epidemiological investigations repeatedly link PM_{10} exposure to adverse cardiovascular events in individuals with advanced atherosclerotic disease. Medical research from our laboratory and other laboratories demonstrates that the atherosclerotic plaques in an individual undergo destabilizing structural changes as a consequence of exposure to PM_{10}. Combined, the data suggest that an individual will experience the progressive worsening and destabilization of their atherosclerotic plaques as a consequence of PM_{10} exposure. Now imagine an event that results in an increase in PM_{10} levels, such as a forest fire or a smog day in a large city. Epidemiology investigations and medical research suggest that at this point there will be a decrease in heart rate variability and an increase in circulating white cells and cytokines, and an increase in heart rate, cardiac arrhythmias, systolic blood pressure, arterial vasoconstriction, plasma viscosity, platelet activation, and fibrinogen levels. Combined, all of these factors result in an enhanced clotting (procoagulant) and enhanced inflammatory state of the circulating blood. What we have now in our hypothetical individual is vulnerable atherosclerotic plaques, increased reactivity of the blood and altered shear stress on the vasculature, a perfect deadly scenario for an acute cardiovascular event to play out as follows: as the blood pressure increases, the flow properties of the blood may change, and a vulnerable atherosclerotic plaque, whose endothelium has lost its extracellular matrix and had its surface shape and contours altered by emigrating foam cells, may rupture or break. The increased blood viscosity, fibrinogen levels and platelet activation aid in a large thrombus formation. If the thrombus does not fully fill the blood vessel and block blood flow, it may break off in the setting of increased luminal narrowing and vascular tone and be sent downstream in the progressively narrowing blood vessels. At some point this thrombus will get stuck, blocking blood flow leading to a heart attack or stroke, and potentially the death of the individual. Our hypothetical person has now become one of the 2 million people to die annually from air pollution exposure. The mechanisms involved in the death of our hypothetical person were not only the inflammatory mechanisms, but also the autonomic dysfunction mechanism. We propose that these two mechanisms are not separate; rather they are convergent processes that together lead to plaque destabilization and rupture as a consequence of chronic air pollution exposure.

3. Future actions to reduce the health consequences of air pollution

The World Health Organization predicts that there are more than 2,000,000 premature deaths every year as a consequence of air pollution exposure. This number is far too high, particularly for the friends and family who have lost a loved one. Steps can be taken on several levels to reduce this number. To begin with, through continued epidemiological and medical research scientists can continue to uncover the underlying mechanisms for the high number of deaths. Secondly, measures can be taken at local, national and international levels to reduce the global production of air pollution.

3.1 Research

Since 1952 when so many people died during the London Fog, a great deal of insight about the effects of air pollution has been uncovered. However, scientists still do not fully understand the biochemical mechanisms underlying PM related deaths. Research in this field is needed to expand scientific understanding. These efforts would be made with the hope that greater scientific knowledge can lead to medical prevention of further fatalities.

There are several overarching topics that should be investigated in further detail. The first is understanding the medical effects of individual pollutants, understanding who is at risk, what medical conditions these individual pollutants cause, or aggravate and why. Once this is better understood then efforts need to be made to understand how mixtures of pollutants act, and how mixtures of pollutants condense and modify over time. It will be important to understand if certain pollutants work synergistically to aggravate cardiopulmonary morbidity and mortality. It will be important to understand the acute and the chronic effects of the pollutants to predict subsets of the populations who are at greatest risk. Beyond this it will be important to understand the extent of the health effects of PM exposure on the otherwise healthy individuals in society.

3.2 Reduce PM creation / Increase PM reduction measures

In addition to research, measures can be taken to reduce the effects of PM by decreasing PM production and increasing PM removal from the atmosphere. To successfully accomplish a reduction in PM pollution steps can be taken at all levels of government. There is a great deal of literature already existing on this topic, but here are a few ideas to consider.

3.2.1 Local

At the local level individuals can make choices that reduce PM creation, such as purchasing locally grown food that is not transported great distances, or growing their own vegetables and fruit. Local governments can implement green programs that increase the use of bikes or carpools to reduce the use of cars for short trips. Efforts can be made to help homeowners make better choices in the selection of building materials for new homes, and help individuals make existing homes more energy efficient. Both individuals and communities can take measures to reduce energy waste, thereby reducing PM production. Taking action like bicycle commuting has multiple positive effects such as reducing a person's risk of cardiovascular disease and obesity, reducing the production of PM and saving money on fuel. However, individuals will not commute without bike lanes and safety infrastructure thus this behavioral change needs support from local government.

3.2.2 National

The contribution at the national level comes under two broad categories: financial and legal. The changes that will be required at the individual and local level will require a financial investment. Furthermore, nations should invest in research to understand the health consequences of pollution exposure as well as dedicate money to the development of less polluting technologies. Governments should consider the money they will save on health care expenses as justification for this expense.

The legal category applies to government regulation of industry. Governments need to hold polluting industries responsible for the damage being done to the environment and human health. Though industry will not be in favor of tough regulations in line with the current recommendations of the World Health Organization, the regulations need to be implemented. This may require governments to financially assist companies as they transition to less polluting business practices. The transition will be expensive and challenging, but given the impact PM pollution production is having on human health and the environment, it is a transition that must be done.

3.2.3 International/ global

The contribution at the international and global levels is similar to the contribution at the national level: financial and legal. Countries need to hold each other accountable for the pollution that is being produced. China, one of the biggest suppliers of goods in North America, is also one of the countries producing a lot of pollution. In the international arena, countries need to decide if this is an acceptable situation.

4. Conclusions

Data from epidemiological investigations and medical research strongly suggest that exposure to fine particulate matter air pollution results in deposition of particulates in the lungs, activation of a systemic inflammatory response and alteration of the ultrastructure of atherosclerotic plaques. Air pollution levels can be controlled if individuals make efforts to reduce their pollution production, and governments at the local, national and international levels invest in green infrastructure, and green technology to reduce pollution production as well as invest in ongoing medical research to understand the biological mechanisms underlying air pollution related morbidity and mortality. It will take a coordinated effort to globally reduce the production of air pollution and reduce the effect air pollution has on human health.

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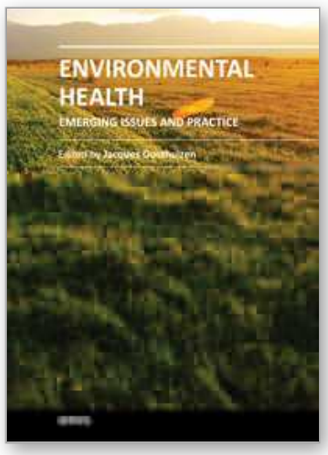

Environmental Health - Emerging Issues and Practice

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Environmental health practitioners worldwide are frequently presented with issues that require further investigating and acting upon so that exposed populations can be protected from ill-health consequences. These environmental factors can be broadly classified according to their relation to air, water or food contamination. However, there are also work-related, occupational health exposures that need to be considered as a subset of this dynamic academic field. This book presents a review of the current practice and emerging research in the three broadly defined domains, but also provides reference for new emerging technologies, health effects associated with particular exposures and environmental justice issues. The contributing authors themselves display a range of backgrounds and they present a developing as well as a developed world perspective. This book will assist environmental health professionals to develop best practice protocols for monitoring a range of environmental exposure scenarios.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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