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A brief history of occupational toxicology

1.1 Occupational toxin exposure in antiquity

There are several activities essential to a civilised society, such as reliable food production as well as some provision for manufacturing and processing goods and foodstuffs. Whilst farming came comparatively late in human evolution, perhaps 8000–10,000 years BC, manufacturing of some recognisable sort appeared even later, when humans started to mine and process various metals. Of course, recovering metal ores from underground exposes the individual to many physical dangers, such as rock falls, floods and toxic gases. However, the significant energy input required for the extraction and processing of pure metals presented new hazards, such as the hot gases and dangers of the molten product. Many ancient cultures soon developed what we might recognise as a production process, where metals were mined, smelted and processed, including copper and tin, which were eventually combined to make bronze, which was more durable than either metal alone.

Whilst the process of smelting is inherently dangerous, neither copper nor tin is especially directly toxic to man. Indeed, the metal that replaced both of them in tool and weapon manufacture, iron, was also not particularly toxic to process in itself. These metals do not tend to accumulate in the body and cause acute or chronic toxicity during normal processing techniques. Lead, however, is very toxic, and the mining and smelting of this malleable and useful metal were probably the first activities where there were significant acute and chronic toxic hazards encountered during its handling. Lead is usually found as its sulphide (galena), which contains silver, so lead production at first was a by-product of silver recovery. Lead usage was fairly widespread before the ascendancy of the Romans, with many ancient peoples such as the Egyptians, using it for a variety of tasks; these included fishing weights, water piping and the basis of a form of early mascara.

Hippocrates (460–379 BC) [1] was the iconic founder of modern medicine, and it has been thought that he was the first to describe occupational lead poisoning; however, this is not actually true [2] as his description was not as precise as some

authors would have it. The first detailed surviving description of lead intoxication appeared (in verse, apparently) around the second century BC, in the physician and poet Nicander of Colophon's *Alexipharmaca*. As the reach of the Roman Empire extended, by the beginning of the first century AD, lead usage increased dramatically. Indeed, the impact on health of any toxic process is directly related to its scale, and the Romans used vast amounts of lead in their grandiose, but impressively durable building projects. For instance, thousands of tonnes of lead were involved in the construction of a siphon unit in the great aqueduct at Lyon [3]. To supply lead on such a scale meant processing which we would even now recognise as 'industrial'. Consequently, it is not surprising that several Roman figures described the appalling environmental impact of lead processing, as well as the toxicity of the actual processes used for purifying the metal. Towards the end of the first century BC, the architect known today as Vitruvius (Marcus Vitruvius Pollio; ~75 BC to ~AD 15) described the severe impact on local water supplies of metal processing, and he stated his opposition to the use of lead piping because of its toxicity to the lead workers, as he noticed how pale they looked. The philosopher and scientist Pliny the Elder (Gaius Plinius Secundus; AD 23–79), writing around 70 years later, commented that lead produced 'noxious and deadly fumes' when it was heated and processed. Pliny also designed masks that could be worn by workers to protect them from fumes. Interestingly, as with many toxins, although the dangers of lead were well documented, it continued to be used on a large scale for centuries after the deaths of its early critics. As we know, lead was used in piping and paints until well into the twentieth century and remains in many houses today, carrying drinking water all over the United Kingdom. Whilst it remains useful as a roofing material, perhaps most remarkably, lead was employed in its tetraethyl form for more than 80 years as an anti-detonation agent in fuels, such as petrol (gasoline); unfortunately, vast amounts were released into the atmosphere via this route. Since its removal from fuels in most countries before the year 2000, this source of lead pollution has declined dramatically in developed economies. Currently, lead is much less of a toxic threat than before, although human exposure in foodstuffs will probably never entirely be eradicated.

1.2 The Middle Ages and the Renaissance: The beginnings of modern occupational toxicology

Although always a crucial part of metal industries, mining in general broadened in scope up to the Middle Ages and beyond, as many more materials were actively recovered from deeper and deeper pits. The mining of coal for energy began in earnest after the thirteenth century, and by the end of the fifteenth century, metal mining to support the armaments industry was growing rapidly, as cumbersome cannon evolved towards more intricate hand-firearms. All this increased demand for iron, lead and copper, along with other metals. In 1473, the German physician Ulrich Ellenbog (1435–1499) wrote the landmark paper *Von den giftigen Besen Tempffen*

un Reuchen (On the Poisonous Wicked Fumes and Smokes), where he described the various toxic processes found in the gold mining industry, which involved fuming acids, as well as lead and mercury vapours. A more systematic exploration of mining and its hazards was then made by another German physician *Georgius Agricola* (Georg Bauer; 1494–1555), who developed a lifelong fascination with these subjects. He even bought a share of a silver mine and published several books on mining and various minerals, including *De Re Metallica* [4], which took him more than 20 years to write and was only published after his death. Although the book's main focus is its extraordinary detail of the methods of mining and metal processing of the time, he did investigate and document many of the occupational hazards of mining, including the various types of pneumoconiosis, such as silicosis, as well as other mining health dangers. Agricola is regarded now as a particularly able and methodical scientist, whose enthusiasm (Section 1.11) and understanding of the value of the observation of phenomena in making appropriate deductions were far ahead of his time.

A contemporary of Agricola was the much better known *Paracelsus*, and variations of his ubiquitous quote “All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy” have adorned many a text and student submission over the centuries. Philippus Theophrastus Aureolus Bombastus von Hohenheim was born in Zurich in 1493. His physician father, Wilhelm Bombast von Hohenheim, became an expert in occupational medicine in much the same way as Agricola, through researching his mining patients' experience. Strongly influenced by his father, young Philippus nevertheless began his studies with the controversial subject of alchemy. Today, the idea of making gold and silver from base metals in an ordinary laboratory sounds as quaint as it is impossible, without the aid of a Nuclear Research Facility. However, as late as the seventeenth century, it was taken deadly seriously, and most of the front rank of scientists at that time, such as Isaac Newton and Robert Boyle, considered themselves alchemists, although in secret.

Philippus Von Hohenheim travelled widely and studied surgery and, through his alchemy activities, chemistry. He began to pioneer the role of chemistry in medicine, rejecting various contemporary ‘cures’, in favour of a more systematic approach to the use of remedies such as opium, as well as metals such as lead and antimony. He advocated the use of small doses of mercury for syphilis, which was essentially the right idea with the wrong agent, as mercury was eventually proven ineffective for syphilis in the 1940s.

Philippus's ideas were revolutionary for his time, and he is credited with not only ‘inventing’ pharmacology, through his concept of dose and how its related to response, but also toxicology and even the idea of the ‘target organ’ for toxicity [5]. Sadly, he managed to combine aggression, certainty, excessive fondness for alcohol, flamboyance and arrogance in his personality and even styled himself *Paracelsus*, or greater than Aulus Cornelius Celsus (~25 BC–AD 50; the Roman author of the medical treatise *De Medicina*). This, combined with contempt for accepted wisdom and a theatrical and sometimes incendiary lecturing style, he ensured that he surpassed all his peers in his ability to make seriously powerful enemies. His drinking

led to fatal liver cirrhosis at only 48 years of age, having spent his life challenging and usually failing to defeat medical orthodoxy. However, although he remains controversial to this day, I think it can be said that he made a significant contribution to occupational medicine, not least through his ideas on the specific mechanisms whereby toxins impact the body, as well as a book on miners' diseases. Perhaps it is characteristic of his personality and ambition that he entitled his last major work, *Die Grosse Wundartznei (The Great Surgery Book)* of 1536, which restored his fortunes and public image.

As mining became more industrialised, many more debilitating conditions emerged, not least vibration 'white finger' and noise-related deafness, which were linked with cutting and boring machinery, as well as toxicity associated with the fumes of explosives and more recently, underground vehicles. In recent times, whilst mining has all but disappeared in the United Kingdom, it remains a major industry in more than 50 countries worldwide, although fatality rates and occupational disease remain several fold higher than other industries [6, 7]. In the United Kingdom, the legacy of 'black lung', which is the form of pneumoconiosis caused by coal dust, continues to blight and shorten the lives of retired miners. As there remains several hundred years of supply of coal under the United Kingdom, it is likely that this energy will be exploited in the future, not by manual labour, but with the application of new technology applied to underground coal gasification (UCG), which can be carried out from the surface using bore holes. Interestingly, the concept of UCG is far from new; one of its early proponents was Lenin (Vladimir Illych Ulyanov; 1870–1924), who sought in 1913 to make presumably irony-free political capital out of the possible benefits of UCG, in claiming that it would free the proletariat from the dangers of working underground in Tsarist mines [8].

The individual who is regarded now as the father of occupational medicine was the Italian physician and Professor of Medicine at the Universities of Modena and subsequently Padua, Bernadino Ramazzini (1633–1714) [9]. He was the first physician to devote his career to a systematic investigation of over 50 occupations, involving visiting places of work and questioning workers. He exhorted his fellow physicians to routinely enquire after occupation, as well as symptoms. His career culminated in *De Morbis Artificum Diatriba (Discourse on the Diseases of Workers)*; first edition, 1700, second edition, 1713). This work described many different occupations, their consequences and ideas for alleviation of the damage and the processes that caused it. Importantly, he not only understood that the various noxious materials, gases and vapours to which workers were exposed were actually responsible for their health problems, but also that unusual specific movements and postures required by the occupation contributed to morbidity and mortality. In this latter area, he was the first to recognise repetitive strain injuries, which remain a workplace hazard today. His work anticipated the Industrial Revolution, where manufacturing grew in scale beyond anything that preceded it, involving large numbers of individuals, vast amounts of processing and long periods of exposure to noxious agents, particularly those related to polycyclic aromatic hydrocarbons (PAHs) from coal and petrochemicals.

1.3 The Industrial Revolution

Whilst it is generally accepted that the Industrial Revolution began in Britain, industrialisation and mining expansion occurred in many other countries, and several scientists around Europe made notable contributions to the emerging science of occupational health in the eighteenth century. Gradually, very early concepts, such as Pliny's ideas on protective measures in the workplace, became re-discovered and reinforced, whilst the understanding of specific links between certain toxins and particular conditions and their mechanisms of toxicity, pioneered by Paracelsus, also gathered pace. The brilliant Russian polymath Mikhail Vasilyevich Lomonosov (1711–1765) outlined measures to be taken to ensure occupational safety in mining in a 1763 treatise, although he could be of a similar disposition to Paracelsus and was imprisoned for eight months for abusing his University's administrators (sounds harsh) and was even briefly forcibly retired by the personal order of Catherine The Great. In England, a major step forward in the understanding of how pollutants from a specific occupation can cause permanent and even lethal injury was made by Sir Percivall Pott (1714–1788). Dr Pott was an extremely well-liked, industrious and technically proficient surgeon, who among many other achievements gave his name to a particular type of compound fracture. The image of eighteenth-century medicine is somewhat tarnished by its obsessions with bleeding, purging and, of course, amputation, for a surprisingly wide range of conditions. However, Dr Pott did his very best with what he had, made highly significant additions to medical knowledge and worked tirelessly right up to his death, which was actually hastened by his devotion to his patients.

Today, in the developed world, many developing countries are criticised for allowing dangerous child labour practices; however, from the end of the seventeenth century in England, after being sold to master chimney sweeps by their parents, boys as young as seven years old were sent up naked into extremely cramped chimneys to clean them. They were sometimes 'encouraged' by the sweep lighting a straw fire beneath them [10]. It was not uncommon for these children to die of asphyxiation, and survivors were treated appallingly, with no access to washing facilities. Hence, they would develop scrotal soot warts, which they would sometimes remove by themselves with a knife. These warts would sometimes become cancerous, usually many years later. The idea of employing children in this way was actually considered repugnant even by the end of the eighteenth century, but was not outlawed until 1842 due to the resistance of the master chimney sweeps. Whilst Dr Pott was not the first person to describe the tumours, he made the link between the soot exposure and the tumours, so becoming first to recognise that a malignant disease was caused by a specific occupation [11]. One interesting and important perception he also made was that because the signs of the disease appeared after puberty, it was commonly ascribed by doctors to venereal disease and thus treated with mercury, which of course made things worse. Such understandable misdiagnosis continues today in areas such as idiosyncratic drug reaction, as well as in occupational health,

and it still costs the patient time, allowing the disease to progress whilst increasing suffering. As the nineteenth century progressed, it became apparent that scrotal cancers usually presented decades after exposure had finished and although such long lag-times in cancer presentation are still studied even today we do not understand all the processes involved. Interestingly, it was realised as early as the 1890s that chimney sweeps' scrotal cancer was very much an 'English Disease' because in every other country in Europe (even in Scotland), sweeps wore effective protective clothing. Tragically, it took more than a century from the discovery of this cancer towards some means of alleviating it, and right up to the end of the nineteenth century, English sweeps were at an eightfold greater risk of scrotal cancer than other males.

1.4 Petrochemicals: The beginnings

Up to Potts's time, human exposure to PAHs was restricted to environmental coal fire pollution of various sorts, such as in chimney sweeping. As the second half of the nineteenth century progressed, the growing industry of coal distillation produced a variety of different products, ranging from thick, tar-like pitch, to paraffin waxes and various solvent mixes, such as naphtha, creosote and anthracenes. These agents were used as fuels and lubricants of various kinds in many emerging light and heavy industries in England and Europe. It gradually became apparent that workers exposed to these agents, either through their extraction, combustion or usage as lubricants, were suffering from the same scrotal cancers as chimney sweeps. A report by von Volkmann in 1875 [12] revealed that men working with tar distillates were at risk of these cancers. Over the next 25 years or so, many other workers, such as mule spinners in the Lancashire and Yorkshire Cotton Industry, as well as Oil shale workers, were seen to be at risk of petro-chemically induced cancers. The Oil shale business became uneconomic in the 1870s when oil imports began to grow, and only the appearance of modern processing technology and the high price of oil have made shale extraction viable today. The coal tar and oil distillation industry continued to grow from the turn of the century and was particularly well established in Germany, where by 1913 just one factory at Elberfeld run by Bayer employed 8000 workers. It is also worth noting that the number of technically advanced spin-offs of the tar-distillation industry, such as the dye, fuel and tyre industries, was also growing; indeed, the Elberfeld factory employed 330 skilled chemists with university-level educations.

The plight of the mule spinners, however, is a good example of how a combination of specific working practices, environment and toxin exposure can cause an unusual neoplasm. A 'mule' was a long machine invented by Samuel Crompton in the late 1770s that could spin cotton (or other fibres) into yarn, and it was operated by a 'minder' and usually two boy 'piecers' who acted to repair threads when they broke. Each cotton mill might have up to 60 mules, and the basic design did not change until the 1970s when the industry died out in the United Kingdom. From

the early 1900s to the 1920s, rates of scrotal cancer in mule spinners reached such levels that strenuous efforts were made to try to understand the process in order to prevent it. By the 1920s, the idea that mineral oils were carcinogenic had reached common medical knowledge, as the carcinogenicity of tar had been clearly demonstrated when it was painted onto rabbits ears [13]. By the 1930s, the carcinogens in tar were narrowed to dibenzanthracenes and 3,4-benzpyrene. In 1926, S.A. Henry (1880–1960) reported that the scrotal cancer developed by the mule spinners was caused by lubricating mineral oil thrown off the machines. Later studies determined that the location of the worker's cancers was probably linked with their tendency during their work to lean across an oily 'faller bar' to repair broken fibres. This was exacerbated by the heat of the mills, where the spinners wore very light clothes which offered no protection against the oil seepage towards the scrotum, and these clothes were extremely contaminated with oil on a daily basis. The skin of the scrotum is 80 times more permeable to toxins than skin on the rest of the body, which promoted the penetration of the oil into tissues. In addition, a mist was formed by the fibres and oil spray, which combined with intense machine noise, suggests a very unpleasant working environment. Indeed, to digress slightly, my closest friend's mother, Mrs Vera Winn, worked in a cotton mill, and she said the only way to communicate was by lip reading; the machines were so loud. The noise levels in many industries were sufficiently high for manufacturers such as Ford in the United Kingdom to make substantial one-off compensation payments to many of their former workers as late as the 1980s.

Returning to the subject of oils, Henry's 1926 report presciently recommended that the oils be replaced by so-called white oils which were pure paraffins and guards should be fitted to the machines to reduce oil splash. Over the next two decades, it took a series of papers by Twort and colleagues in Manchester [14] that not only established that the mineral oils used in mule spinning were carcinogenic, but that if they were used for long periods and subject to heat, such as in use in the mules, even more carcinogenic agents would form through the process known as 'catalytic cracking'. Indeed, this is the basis of petrol and diesel fuel production, where larger polycyclics are broken up into smaller agents. Frequent replacement of the lubricating oil would not be a priority for many mills, so the oil's carcinogenicity would gradually increase. It was not until 1945 that the industry was forced to use non-carcinogenic white oils. As you will read later, there are many parallels with the UK automotive industry, which in many areas did not conform to the 1945 standards of the now defunct Cotton industry until the 1980s.

1.5 Petrochemicals and mass production

The petrochemical industry was vastly expanded by the extremely rapid emergence of the new automotive industry over the period from 1900 to the Great War (1914–1918). Henry Ford (1863–1947) successfully adapted the assembly line concept

used in the Chicago meat industry, and together with his durable Model T Ford design (you could reliably commute in one today, once you got used to the pedal arrangement), he was responsible for the phenomenal early growth of automobile manufacturing capacity. Indeed, although five million Model Ts had been produced up to 1921, this figure was actually doubled only three years later. By the 1930s, Ford's River Rouge complex at Dearborn in Michigan employed more than 100,000 workers. Such a growth stimulated other industries which were dependent on supplying the car and truck industry, which was well paid in comparison to most other manual labouring jobs, thus despite the repetitive nature of the assembly line, jobs with Ford were keenly sought.

The sheer scale and diversity of the different components of a motor vehicle spawned a vast engineering empire which involved subsidiary factories which employed various paint delivery systems, as well as metal casting, grinding, boring, plating, milling, stamping, broaching, heat-treating, welding and polishing processes. This meant that all these light engineering processes had their own often wasteful oil and lubricating processes, which ensured the machine tools operated efficiently. In addition, thousands of tonnes of different chemical solvents were involved in preparing (such as degreasing) metals for all these processes. Large amounts of component welding, cutting and stamping took place alongside the routine machine tool operation, as well as engine testing without rocker covers. All this created a dense mix of oil vapour, combustion and welding fumes which formed a thick fog inside the shop floors, which was an environment not dissimilar to the nineteenth-century cotton industry, where the fumes combined with machinery noise, heat and lack of ventilation. Indeed, workers' testaments from the UK and US car industries as late as the early 1980s described that the oil and fume mists were such that it was difficult to see more than a few yards. Given that very high oil mist levels in car factories before World War II resulted in workers suffering from bronchitis and other direct lung irritation-based complaints, it had been appreciated by plant managers even then that it was necessary to restrict atmospheric oil contamination. Gradually, the industry began to control the mists through better ventilation and more efficient machinery as the 1950s and 1960s progressed, although oil and fume mist levels were not by any means eliminated.

As with the cotton industry, the key danger of the mists was the carcinogenic nature of the oils used. In the United Kingdom, the automotive industry was slow to appreciate this risk, and it was not until the early 1960s that it belatedly realised that aromatic hydrocarbon content in a mineral oil was the chief determinant of its potential carcinogenicity. Unfortunately, as will be described in Chapter 4, mid-1960s recommendations that cutting fluids used to machine car components should not contain mineral oils with any aromatics, were not heeded. Automobile industry workers today often do not engender great sympathy in the United States and United Kingdom, partly because of historically poor labour relations and a reputation for militancy, allied to what was still in the 1970s and 1980s considerably higher pay than many other occupations. However, up to the 1980s, the available

evidence and testimony suggest that it was not a pleasant industry to work in and it was resistant to lessons learned from other industries over issues related to toxic oils. This meant that metal cutting right into the late 1970s involved exposure to carcinogenic aromatic hydrocarbons, as well as to nitrosamines liberated from cutting fluid emulsions containing amine antioxidants. This translated into higher levels of cancers related to other industries. In a General Motors subsidiary factory at Coldwater Road near Flint, Michigan as late as 1980, several workers noticed that the mice in the plant were developing visible tumours, which they reported to their Union. Some mice were caught and tested, revealing that the tumours were cancerous. The metal-plating processes which the plant specialised in became outmoded with the advent of various plastic replacements and the plant was closed. However, it left a considerable number of ex-workers who had developed lung cancers at comparatively early ages.

The car industry has responded to these hazards in some ways that are akin to how armaments industries adapt to wartime, by changing manufacturing to reduce labour-intensive and expensive grinding, cutting and milling of components, in favour of stampings and mouldings which can be automated to the point where men are usually no longer in contact with toxic agents. Paint shops are fully automated and sealed, and volatile aromatic solvent paint bases have been replaced by safer and more environmentally friendly water-based systems. The industry remains profitable as although safety has been increased, costs have been reduced partly because fewer workers are often employed as a consequence. Car factories have evolved to the point that many manufacturers invite customers to watch their cars being assembled. However, as new processes are introduced in the industry, such as the increasing use of epoxy resins to bond metals, followed by some welding, this can create hazardous fumes which have not been fully investigated to date. In some factories, up to 50 different adhesives are used in the assembly process, and it has been reported that the famous 'new car smell' might be somewhat more problematic than was previously envisaged.

1.6 Aromatic amines: Tyres, dyes, explosives and cigarettes

The coal tar distilling business of the mid-nineteenth century gave birth to several industries as mentioned in section 1.4, mostly through a key discovery made by the English chemist, William Henry Perkin (1838–1907). Young Perkin was earmarked as a potential architect by his father, but became obsessed with chemistry when still a teenager. Indeed, the sheer ferocity of his interest in the subject led him to build a laboratory in his house, as he was too busy at college to pursue all the chemistry that interested him. Whilst trying to make a synthetic antimalarial, he treated aniline distilled from coal tar with the oxidising agent potassium dichromate and made a rather disgusting-looking black precipitate, which Perkin

subsequently discovered was actually an effective purple or, as the French named it, 'mauve' dye. He then set about inventing the industrial process to make this dye in quantity and became the father of the aniline-derived dye industry, despite many authority figures insisting that he would never be able to scale up his inventions successfully. Perkin sold his factory in 1874 for a tidy sum, which allowed him to spend the rest of his life as what could be perhaps termed today as a postdoctoral dye researcher. He was by all accounts an extremely pleasant individual, hugely respected by his peers and who was devoted to his work and his family.

Aniline dyes were successful in the clothing, leather and many other industries due to the dye tending not to run and also that it would colour the surface of the item evenly and retain elements of the natural features of the cloth. As the dye industry became a large-scale employer, particularly in Germany, it became apparent that working in the industry could lead to developing bladder cancer. This was first reported in 1895, by the German surgeon Ludwig Rehn (1849–1930) [15], who investigated cases in a German aniline factory. With the beginning of the Great War in 1914, the German dye industry was turned over largely to explosives manufacture, and incidentally, their large watch and clock industry was given over to making timing mechanisms for explosive devices of various types. The difficulty in obtaining German-sourced dyes and the US entry into the war in 1917 led to the establishment of the industry in the United States by companies such as Du Pont (E. I. du Pont de Nemours and Company) in Wilmington, Delaware, and within a couple of decades, bladder cancer rates had dramatically increased in US dye workers in the Du Pont factories. By the late 1940s, it was established that rather than aniline itself, it was various aromatic amines linked to aniline processing which were responsible for the cancers, particularly β -naphthylamine (BNA) and benzdine. These agents and several other aromatic amines remain among the ever-growing list of chemicals and other agents which are accepted as human carcinogens [16]. From the early twentieth century, BNA was used in tyre manufacture as an antioxidant to slow the natural hardening and physical deterioration processes seen in automotive tyres, but its use was banned in the United Kingdom in 1949, and it was replaced by phenyl-BNA (PBNA). BNA continued to be manufactured around the world, such as in China and other developing countries and their bladder cancer incidences duly rose after the 20–30 years' cancer latency period elapsed. Whilst a perhaps small proportion (around 4–10%) of bladder cancer cases are probably linked to other polycyclic aromatics, such as benzopyrene, it has become apparent that most bladder cancers contracted in various industries are linked with BNA and benzdine derivatives, which were either used in chemical processes or were formed during combustion of petrochemicals, such as in coke ovens and in metal smelting.

It is useful to remember that although occupation is linked with bladder cancer, the major cause of the disease is actually tobacco smoking, although the specific chemical responsible remains BNA. As will be discussed in Chapter 4, these

multiple sources of BNA and the possibility of its formation from supposedly safer substitutes can complicate the assessment of causation in cases of occupational bladder cancer.

1.7 Contemporaneous knowledge

So far in this brief introduction to occupational toxicity, a pattern can perhaps be discerned. An industry gradually emerges, using certain machinery, processes, work practices, chemicals and design of premises. This industry then becomes increasingly successful and powerful, through engaging whole communities in long hours of manual labour, which not only supports those communities, but makes certain individuals and their fellow investors incredibly rich and politically influential. Over time, it is noticed that the process of manufacture is associated with an abnormal morbidity and mortality in the workforce, and medical research is carried out on both the effects on the workers and basic research proceeds on the specific nature of the hazard. The knowledge of why the agent is toxic gradually surfaces in the scientific and medical press, which filters through to publications related to the industry and sometimes through to the local and national press. At some point during this process, which may last decades, the industry might take heed that its activities are causing mortality and morbidity, and it 'does the decent thing' by setting aside money to compensate the workers injured by the process and changing the activity and/or agent which is responsible for the problem.

Of course, this is far from an ideal situation, as it is clear that many workers will have been injured before action is taken, and their path to individual compensation is usually immeasurably more painful, expensive and protracted than those that might benefit from the first compensation initiative. Many industries over the last two centuries have followed a similar course to that described above, as often the nature of the specific mechanisms whereby a chemical or industrial process injures an individual chronically was simply not known until the sheer scale of the process or the chemical usage for a considerable period of time reveals the risk and the mechanism is determined by medical and scientific personnel. Indeed, a key factor in all claims for compensation from an employer or more likely, their insurance company, is linked to 'contemporaneous knowledge'. Should the employer have known that the agent was a hazard at the time the workers were exposed and if they did know, then why did they not take steps to protect them from the hazard? In real life, there are many shades of employer culpability, and to be fair, workers themselves can be notoriously resistant to complying with Health and Safety measures. In addition, a charitable view is often taken, where there can be significant lag-times between large and cumbersome organisations 'digesting' information which is ascribed to a combination of internal rigidity and poor communication.

1.8 The pursuit of truth

It is easy for us today in the developed world to pass withering judgement on the horrors of our industrial past, without perhaps considering the activities of an industry in the context of the standards which were held at the time. Today, it is much easier to champion the emancipation of illegal child labourers in the United Kingdom, than, say in India, China or Vietnam. As we saw earlier, the protracted resistance to the banning of child chimney sweeps in the United Kingdom was probably partly a result of the somewhat schizophrenic early Victorian attitude to children, where childhood could be idolised, whilst children were routinely maltreated. In Germany, the work of Johann Frank (1745–1821) and later in England of Thackrah in 1832 [17] as well as Chadwick a decade later [18] not only revealed the suffering of many in various trades which were hugely injurious to health, but also demanded passionately that this situation be changed in direct terms. These authors and many others in the industrialised nations of the nineteenth century drew attention to the fact that life expectancy was strongly linked to social class, and alongside deprivation and poor living standards, occupation was a powerful influence on mortality and morbidity.

Changes in social attitudes had to occur before there could be recognition of workers' rights, and this process was and remains agonisingly slow. However, many industries carried on exposing their workers to conditions which were unacceptable even by the standards of the time. In the United Kingdom today, whilst we assume we live in a progressive and just society, situations emerge where a group of individuals are exposed to a sustained injustice, which is only confronted once a courageous individual has exposed the perpetrators to public opprobrium. However, it has almost become a cliché in real life, cinematic and televisual entertainment that this individual was probably actually sent to investigate the problem, but often meets determined resistance from powerful and influential quarters, sometimes even from those who entrusted them with their mission in the first place. Likewise in occupational medicine, institutional resistance to investigation and clarity is often to be expected, and stratagems must be evolved to determine the truth to help the worker. As far back as 1848, the Prussian doctor Rudolf Virchow lost his office, job and salary for revealing the extent of the social depravation in Silesian miners when he was actually sent to investigate a medical emergency in the area. Even into the mid-twentieth century, workers in industrialised countries who reported occupationally linked disease risked being regarded as lazy or feckless, and even talking to a health-care professional could lead to dismissal. Companies and organisations refused to release details of their workers' health and obstructed anyone who sought such information. Occupational medical pioneers in the United States such as Alice Hamilton (1869–1970) could only build a picture of the extent of lead poisoning in many industries through what was termed 'shoe-leather epidemiology' [19]. This involved tirelessly tracking down workers' records and persuading individuals in numerous industries over many years to report their symptoms and working

practices which caused their ill-health. Nearly a century later, Figueroa and Weiss [20] employed similar techniques to reveal the carcinogenicity of bischloromethyl-ether in spite of the determined resistance of the chemical industry.

Sadly, there remain many examples of employers who did know of the hazards, yet chose not to protect those at risk. Worse still, there were many whole industries which were collectively aware of the devastating consequences for their workers of handling certain agents, and they were not only resistant to providing protective equipment, but they were also extremely active in escaping their liabilities and responsibility for their worker's plight. The next sections recount a brief history of three industries which perhaps typify this somewhat extreme situation; the early twentieth-century radium dial industry, the asbestos business and, of course, the hat industry.

1.9 The 'Mad Hatter'

Lewis Carroll's depiction of a somewhat bizarre milliner in *Alice in Wonderland* (1865) has now passed into popular culture as a terrible example of occupational toxicity related to the use of mercury to treat felt. The truth could well be more complex, as the book was published in a period where it has been latterly argued that there was actually little common perception of hat making as particularly dangerous, despite some contemporary medical reports of mercury poisoning associated with handling hat making materials. Indeed, it is said that Carroll's inspiration may have been a slightly unhinged but creative individual known as Theophilus Carter, a top-hatted Oxford furniture dealer who apparently invented an 'alarm clock bed' which woke the sleeper by physically turfing them onto floor. This inspired invention could yet find a lucrative online market today with the parents of particularly indolent teenagers. It is believed now that the phrases 'mad as a hatter' or 'mad as a March hare' pre-dated *Alice in Wonderland* by several decades. It appears that the story of how mercury became involved in the hat business is also somewhat confused and convoluted.

Until the end of the seventeenth century, hats were made from various woven fibres, but the use of fairly poor-quality animal skins (particularly rabbit) to make hat felt began in France and necessitated some processing to make the material resistant to rotting, by altering the protein structure as well as firstly removing the fur or hair from the hides. The leather industry used various substances including urine to remove hair from the hide, and the emerging hat industry followed a similar practice, until legend has it that the urine of a worker under mercury treatment for venereal disease had the best results. This was known to the French as the *secretage* and the industry was dominated by Huguenots, who were effectively hounded out of France after the 1685 Edict of Fontainebleau withdrew their freedom of religion. Hence, they migrated to England, along with their expertise in hat-making. The *secretage* involved using mercury nitrate to shrink and lift the fur off the hide. The fur would turn orange, giving the name of 'carroting' to the process [21], which

seemed to die out after the end of the eighteenth century in England, only to resume around the 1840s.

The epicentre in North America of the hat industry from the early eighteenth century was Danbury in Connecticut, where beaver was first used, and interestingly, their hides did not require mercury to treat them to make high-quality felt. However, as with the North American Bison, over-hunting virtually wiped the beaver out, so rabbit and other small animals were drawn into the highly profitable Danbury operation, and at its peak, mercury nitrate became an essential of the processing of more than five million hats per year [22]. The hat industry in the United States was associated with debilitating toxicity from as early as the 1830s and from the 1860s all the way to the 1920s; a succession of medical reports drew attention to the damage mercury caused to hatters' health. Little was done to prevent it, by either protecting the workers or by seeking alternative processing materials.

As early as 1874, a method appeared to replace mercury and towards the end of the nineteenth century, there were several more methods available [23, 24]. However, as with the master chimney sweeps, the industry was highly resistant to change, and it carried on using mercury to the point that it had to be banned by the US Government in December 1941, although this initiative may have owed more to the coming need for mercury in the munitions industry, rather than concern for workers. Even today, the legacy of mercury use is the extremely high environmental mercury pollution in areas where the hat industry flourished, such as Danbury [22].

The effects of mercury on those who worked in the industry were appalling. Many developed unpleasant central nervous system and peripheral effects, including a staggering gait, severe tremors and often extreme irritability with unpredictable behaviour which must have made them impossible to live with. Those most affected also suffered from visual problems, drooling and even hallucinations. The 'shakes' were sometimes even identified with a particular area where the hat industry was very large, entering the local language as the 'Danbury Shakes'. In the United Kingdom, a report on a worker who used mercury nitrate to process animal hides who was admitted to Guy's Hospital with mercury poisoning in 1863 is interesting, as it locates the use of mercury in England from the end of the 1850s, as the individual had only been working with the toxin for four years. This also has to be seen in the context of mercury toxicity, as neither the metal vapour itself nor an aerosol which contains mercury ions is even the most toxic form of the metal. Organo-mercurials, such as methyl mercury, are especially neurotoxic, as they are lipophilic (fat soluble) enough to penetrate the blood brain barrier. This, combined with the relatively short period of exposure prior to debilitating symptoms, suggests that the scale of daily worker exposure to mercury in the hat industry must have been phenomenal. Whilst mercury toxicity was made a notifiable disease as early as 1899 in Britain, even as late as the 1930s, several studies failed to link clinical symptoms of mercury poisoning with urinary metal levels, probably due to crude analysis techniques. Eventually, a group in Milan published a study in 1953 which showed that more than a sixth of workers in the industry showed mercury poisoning. Ironically, not so long after mercury use was banned in the industry, changes in fashion virtually eliminated the felt-based hat industry after the 1960s.

As mercury usage receded in the moribund hat industry, the metal found a use as a catalyst in the formation of acetaldehyde, a key component in plastics manufacture. Methyl mercury was a by-product of this process and the Chisso Corporation dumped up to 150 tonnes of this potent neurotoxin and teratogen into Minamata Bay in southern Japan from 1932 to 1968. The ensuing human and environmental catastrophe cost more than 1700 lives and damaged the health of two million people [25]. There was so much mercury present in the sludge of the factory's wastewater canal, that it was commercially viable for the Chisso corporation to recover, which they duly did. The clean-up operation cost nearly \$US400 million and took 14 years, and the residents of the bay continue to suffer and legal action has not yet been resolved. Another organo-mercurial agent, phenyl mercuric acetate, was used in processes which exploited its antifungal effects, such as in latex paint manufacture (until 1990) and as a seed dressing. It was also used to catalyse the curing of polyethylene flexible flooring, which was used in thousands of school gymnasias from the 1950s to the 1970s [26].

Although many countries have banned mercury usage as a pesticide, it is still used to preserve vaccines, in dental amalgams and particularly destructively, in small-scale gold mining. In this latter application, although systems have been developed to recycle the metal and reduce environmental damage, there remains widespread ignorance amongst workers handling this metal, as to its severe impact on health [27].

1.10 The 'Radium Girls'

Whilst this book is concerned with the evaluation of causation linked with occupational toxins such as metals or petrochemicals, no brief history of occupational toxicity is complete without reference to one of the most poignant occupationally linked tragedies, that of the 'Radium Girls'. Today many of us have watches, mobile phones or various electronic reading platforms which allow perusal of life's latest fascinating developments in total darkness and probably even underwater, for essentially unlimited time. Towards the end of the Great War, the idea of soldiers being able to read a watch or an instrument panel at night was a remarkable innovation, and it was achieved through a paint called 'Undark', which was a mix of radium and zinc sulphide, where the alpha and beta particles from the radium would cause the sulphide to emit a faint glow. This innovation was the product of an ex-laboratory assistant of Thomas Edison, William Joseph Hammer (1858–1934), who combined several careers as a soldier, inventor and tireless promoter of all things related to radium. However, 'successful businessman' was not part of his portfolio, as he did not patent his idea, which by 1920 had led to more than four million clocks and watches produced with radium paint dials. The War had propelled radium-sourced luminous paint towards its vast market, and the Radium Luminous Material Corporation was the first organisation to exploit this idea on a large scale. They became the US Radium Corporation and by the early 1920s, the young ladies in their factory in New Jersey were trained to paint numerals on watch dials by instructors, who showed them how to use their lips to make a fine point on the brush

to allow the accurate formation of certain awkward numbers, such as 8, 2, 3 and 6. The instructors in the watch factories would consume the radium paint during the demonstration, somewhat eerily echoed 40 years later in the Vietnam-era news footage of a US Air Force Officer drinking a cup of Agent Orange (see Chapter 5) out of an aircraft tank to demonstrate to his men that it was harmless.

Whilst the women in the factories became massively contaminated with radium and even sometimes used it to paint their nails and even their teeth with it to impress the unwary in the dark, it seems the owners of the factory and their senior personnel were well aware of the toxicity of their product, which is not surprising, as US Radium was started by medical doctors. The Company scientists actually took the same precautions we take today to shield themselves from the danger. The 'Radium Girls' gradually became sick, as the metal mimicked calcium and accumulated in their bones, particularly their jaws; indeed, their terrible injuries were first recognised by a dentist, Theodore Blum [28]. US Radium, in their efforts to escape responsibility for this tragedy, acted in a way that can only be described as stomach churning, with deliberate and persistent attempts to falsify reports and to draw out the court process, knowing that the women were unlikely to survive long enough to collect much compensation. Indeed, during the court case, some of the women did not have the strength to move their arms enough to take the oath. Only a public outcry allowed them any real financial settlement at all, as the workers were not members of a union and had to organise their cases themselves [29]. A medical report described how contaminated many of the workers were, with many having been exposed to thousands of times the recommended safe dose of radiation. Their clothes and bodies were heavily contaminated to the point of luminosity, as indeed was the discoverer of radium herself, Marie Curie. To this day, the double Nobel Prize winner's domestic cookbook is too radioactive to read without protective equipment. There were many thousands of women employed in various factories using radium paint, and it is unknown how many died prematurely from its use.

1.11 Asbestos

Perhaps the best known and documented of the various industries which are known to be purveyors of disability and premature death is the Asbestos Industry. Interestingly, the properties of these silicate mineral fibres have been known since antiquity, with several accounts in existence of various potentates impressing their guests by cleaning their asbestos tableware by throwing it on the fire, presumably with the ancient equivalent of a theatrical flourish and a smug visage. Pliny left an account of these fibres' many uses, and the Chinese were mining it in quantity by the thirteenth century. The great Georgius Agricola investigated it, partly and somewhat eccentrically, by describing its taste. By the mid-twentieth century, it had found its way into millions of products, ranging from cigarette filters (obviously), brake linings and clutches, through to myriad lagging and building products. Indeed, it has been possible to have a fireproof suit made since 1820.

There are six fibre types recognised as asbestos, with only three ever being produced in quantity. The hardest and straightest fibres are amosite (brown asbestos) and crocidolite (blue asbestos), and these have long been perceived as the most dangerous. They damage the lung because they cannot essentially be removed once they reach the alveoli, and through a combination of the creation of active reactive oxygen species and immunologically mediated damage, they can cause either/or the destruction of the lungs by inflammatory disease (asbestosis) or malignancy, particularly mesothelioma. This condition has killed many hundreds of thousands around the world, as well as the Hollywood star Steve McQueen (1930–1980), one of the protagonists in what is arguably cinema’s premier car chase [30]. The vast majority of asbestos used was chrysotile (white asbestos), whose softer, snake-like fibres were believed to be less hazardous than the blue or brown variants. However, in practice, all manifestations of this mineral are toxic, carcinogenic and are unsafe at any level.

Whilst world consumption peaked in 1973 [31], the toxicity of these mineral fibres was first reported 75 years previously by a UK Factory Inspector, Lucy Deane. She and her colleagues made the link between the ‘glass-like jagged nature’ of the microscopic appearance of the fibres and their ‘evil effects’ [32]. Soon after, a Charing Cross Hospital doctor, H. Montague Murray, examined an asbestos worker and found severe pulmonary fibrosis. After the man’s subsequent demise, Murray testified at a Compensation Committee that he found asbestos fibres in the patient’s lungs and that they were the major cause of his death. The man had worked in a ‘carding room’ and told the doctor that of the 10 people who had worked with him in that room, he was the only survivor [33].

Over the next few years, progress in exploring asbestos’s lethality was slow, although as early as 1918, it was impossible for asbestos workers to obtain life insurance from some companies in the United States. It was not until 1931 that regulations appeared in the United Kingdom to safeguard workers from the hazards of the mineral and in 1932, a report from the Inspector of Factories recognised asbestos’s role in asbestosis. Incredibly, despite a series of official medical reports in the United Kingdom over the 1950s and 1960s damning the mineral, blue asbestos was only banned in 1985. I remember the 1982 Yorkshire Television documentary on those who worked in Cape Insulation Limited’s Acre Mill in Hebden Bridge in Yorkshire, UK, from 1939 to 1970. The debilitation and hopelessness of the workers was appalling to see. Forty-five years after the Mill was closed, the Company eventually did establish a fund to compensate ex-workers, although it was estimated that more than 750 ex-workers had died from asbestos-related illnesses by 2003. This is all the more remarkable, as at its peak, the factory employed only 580 people. It was apparent that unlike other industrial diseases, where only certain individuals might be susceptible to the effects of handling a product, it appears that like mercury and radium, everyone is susceptible to asbestos. The mineral, almost entirely as chrysotile, is still mined around the world and remains in use in considerable quantity. Indeed, the focus of its production and usage has shifted dramatically over the past few decades to developing economies, primarily China,

India, Russia and Brazil, which account for 66% of current world production. Even in the developed world, asbestos may well be probably part of a wall or lagging a pipe, perhaps even not too far from where you are sitting now. However, as long as you can resist the urge to bore holes in the wall or sand the pipe down, it is highly unlikely that you will ever suffer any health impact from asbestos, as it almost exclusively affected those that worked with it. The asbestos industry in general is a byword for its reluctance to acknowledge its culpability in its workers' suffering, and as an industry, it could be justly described by the famous phrase 'the unacceptable face of capitalism'. It is still extremely active in protecting its interests [34], and it effectively 'owns' enough scientists to fight its corner, rather like a malevolent and loathsome infection. Asbestos is by a large margin, the worst occupational toxin ever [35] and its devastating health and financial impact will continue for many decades to come. Many would say that asbestos is now probably the most hated substance on the planet.

1.12 Occupational toxicity: Medicine and science

Occupational medicine ideally should be focussed in the prevention of mortality and morbidity, through enforcement of basic principles of industrial hygiene, which are in turn informed by medical and scientific principles which describe the nature of the hazard and the steps required to make it safe to work with. So in a perfect world, a new manufacturing process should be examined in detail by representatives of the manufacturing process, as well as scientists and medical personnel to uncover any risks to worker safety. Appropriate measures can then be devised and incorporated into the process which ensures that workers are fully protected, before the process is scaled up and begins in earnest. As has been described earlier, too often, the process of occupational medicine is retrospective and begins with ignorance, where doctors meet a set of symptoms with which they are unfamiliar and may not at first follow Ramazzini's exhortation to ask about occupation. In the case of 'Phossy Jaw' and also beryllium poisoning, many workers in the safety match and mining industries suffered from these diseases and doctors had very little, if any, worthwhile knowledge of these conditions, and medical training does not often explore occupational medicine in any depth [19]. Hence, many cases of occupational health damage require a team of experts to investigate and ultimately facilitate the victim's legitimate claim for compensation. Medical examination should initially record the victim's symptoms, and if the doctor is familiar with the industry and its impact on health, he or she can sometimes associate these with the industry. However, this is often not enough to ascribe causation, as many toxic effects can be mimicked by other diseases which are acquired through other means. It is now accepted that 'causation', that is, exactly how the toxin impacted the patient and led to their present condition, should be investigated for a specific case by an individual who has experience in either (sometimes both) the medical or scientific aspects of the toxin or disease.

Whilst there are many examples of expert testimony which have highlighted the dangers to workers, such as the work of von Volkmann for tar distillers and Alice Hamilton for many other trades, experts can sometimes be less than truthful, as we have seen in the Asbestos industry particularly, usually due to company or government pressure. At the other extreme, US Radium's first attempt at 'expert testimony' involved using their own toxicologist under blatantly false pretences, to certify that a transparently sick individual was healthy. When they did ask for an external expert report from the Harvard physiology professor, Cecil Drinker, they were very unhappy with its damning contents and falsified it. Alice Hamilton encouraged Drinker to publish his report which he did, even though the exceedingly wealthy and well-connected US Radium threatened legal action.

The prospect of litigation is daunting to anyone, and the behaviour of an organisation in this context is often related to the perception of ownership of the intellectual property of the report. If an organisation funds a report, it can believe that it has absolute legal control of the information unearthed [19]. Therefore, if this report is published without authorisation, the organisation may well have the means and the will to pursue the expert legally to enforce its position. Various laws, particularly UK libel law, can lend themselves relatively easily to the pursuit of individuals by powerful organisations, and the sheer expense of the process can bankrupt the individual, their supporters and even their publishers. In the United Kingdom, the key stage appears to be whether a statement or statements are viewed as allegations of 'fair comment' or 'fact'. 'Fair comment' may not be a problem, but if a statement is viewed by a judge as an 'allegation of fact', then this requires the defendant (the individual who made the allegation), rather than the claimant (the organisation), to prove the accuracy of their statements, so it pays to be extremely careful over the wording of an expert report [36], and it is perhaps not surprising that many large corporations and government-related organisations have been able to intimidate scientists and medical personnel. Many years ago, I contributed some comments over the health risks concerned with the process of extracting a particular metal in a substantial local facility to a journalist who published a decidedly inflammatory article in the local free press on the subject quoting my comments. The facility managing director almost immediately telephoned me in what can only be described as a Caledonian Fury and demanded that we should meet at the University to discuss how I was 'endangering 600 people's livelihoods'. I agreed to meet him in the presence of my then line manager and the managing director insisted aggressively that I recant my statements. He then dramatically produced a prepared statement that I was to sign to the effect that I was withdrawing my comments. I pointed out that I had merely quoted journal articles that were in the public domain and I produced some copies for his perusal, which he neglected to accept. He then departed in high dudgeon, emitting various dark legal threats. The statement was sent to me again in the post some days later, and I returned it unsigned, restating my position. The managing director then contacted the Vice-Chancellor of my University on more than one occasion and demanded that I should be sacked; the Vice-Chancellor eventually explained to him in apparently direct terms that no action would be taken against me and perhaps he should cease and desist, which brought the matter to a close.

In my case, I was supported fully by my institution; however, other scientists have not enjoyed such backing and have been put under unbearable pressure by various industries, the media, government and other organisations, sometimes with tragic consequences.

1.13 Health and safety today

Whilst it is sometimes fashionable to criticise Health and Safety organisations for overzealous enforcement of various legislation, in the light of even this brief history of occupational toxicity, such zeal is not necessarily a bad thing. In the developed world at least, the tragically long delays between the identification of a toxin's potential role in human morbidity and mortality should now be a thing of the past, as most organisations have access to the latest research and various techniques for monitoring workers' health, to ensure that the use of hazardous agents is fully investigated and that workers health is of paramount importance, if only for financial reasons. However, there remain many organisations, both large and small, which refuse to acknowledge their duty of care to their workforce and whilst many believe that this no longer occurs in developed countries and is now exclusively the part of so-called third-world sweatshops in various eastern boom economies, some of the cases described in this book will hopefully disabuse them of this impression. There remain vulnerable groups of workers in developed countries who can be exploited and exposed to hazardous agents, either through language difficulties or ignorance. In developing countries, the hunger for wealth generation and employment, coupled with a ruthless exploitative 'ethic' which would have impressed many nineteenth-century stove pipe-hatted capitalists, can lead to horrifying worker morbidity and mortality. Indeed, as we will see in Chapter 6, since many of the products of eastern economies are not even safe for the user, so it is sobering to wonder how they are manufactured and under what conditions. Some workers have even smuggled out letters asking for help hidden in their products, to be discovered by consumers overseas [37]. Perhaps more than ever, experts in their scientific and medical fields are needed to engage with cases where their knowledge may be of benefit to an individual, or individuals, who have been harmed by their occupation.

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