

Paget's Disease – is Arsenic the cause?

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Biographical Note

Now retired, I was previously involved as Head of Planning for some very prestigious worldwide construction projects – a dam at 4,400m altitude in Peru, the first ever building spanning a dual carriageway in the city of London, the new Kuala Lumpur International Airport and both new terminals 5 and 2 at Heathrow Airport. Most specialists tend to work in silos, and my skillset is an enquiring and challenging mind with the ability to always keep in mind the overall objective, whilst delving into the detail in those silos and linking interfaces, understanding the impact these have on a project. I am proficient at giving presentations, having given these in both work and university environments (to MSc students). I believe that my great uncle was involved in contributing to the greatest number of cases of Paget's Disease ever recorded among women.

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Abstract

Paget's disease of the bone (PDB) is a chronic localized bone remodelling disorder resulting in the overgrowth of poorly organized bone, leading to deformities. As is the case with many diseases, there is a genetic component but there are also environmental factors. Genetic and familial factors are being extensively studied, and these are responsible for between 25% and under 40% of cases, depending on the genetic makeup of the local population.¹ This leaves the majority of cases with an unexplained environmental cause which may also serve as a trigger for the genetic cases. This disease is estimated to affect about 1% of the UK population over 55 years of age, with a greater incidence in men. There is marked geographical variation in the occurrence of PDB. The UK has in the past had the highest incidence of PDB in the world, but the disease is also common in other European countries such as Spain, Italy, and France. It is also found in certain areas of North and South America and Australia, and is still common in New Zealand, which now has a rate that is possibly higher than that found in the UK.

One man who was heavily involved in the manufacture of an arsenic-based weapon known as the 'M' device was the author's Tasmanian great-uncle, Major Thomas Davies DSO, MC. It was during the production of this weapon in 1918-19 that large numbers of young women were exposed to highly toxic arsenic-based chemicals. The manufacture of this weapon was classified, and the existence of the weapon and the factory remain unknown to most historians, even the local history society in Lancaster. Many UK government files, stamped "secret", were examined by the author when researching his family history. It is suggested that this led, some 50 years later, to by far the highest number of cases of female PDB in the locality of the filling factory ever recorded anywhere in the world. Further investigations were conducted to verify the hypothesis that arsenic has been the primary cause of most cases of PDB in all reported disease hotspots, both in the UK and worldwide. This hypothesis also provides support for the reasons more men than women suffer from the disease, why it is more prevalent in deprived areas, and was particularly prominent in NW England. It shows why it is common today in New Zealand and has not declined significantly in Spain and Italy. Demonstrating why PDB is almost unknown in some regions and among certain

populations, it predicts an increase in the future caused by climate change, the industrialisation of South Asia and China, a water shortage, and the increasing demand for copper. The degradation of sea-dumped chemical weapons may become an issue in due course.

Keywords: Paget's Disease of the Bone, PDB, metabolic bone disease, osteitis deformans, arsenic, toxic elements, coal, CCA, skeletal system.

Introduction

In 1977, a team from Southampton General Hospital published the results of a survey of 14 towns in the UK that used routine radiographs to predict the occurrence of Paget's Disease of the Bone (PDB).² A further 17 towns and cities were then added to this list in a report published in 1980 with a particular emphasis on mill towns in Lancashire which showed a high percentage of cases.³ The results were divided into male and female cases, and a combined rate was calculated. The figures were almost certainly underestimates of the true number of cases as for obvious reasons, the figures were only reported for those cases where radiographs had been taken (for any cause, not just PDB). Nowadays there are additional tests such as an alkaline phosphatase blood test and bone scans which would detect more cases of the disease.

The city that indicated the highest number of cases was the small mill city of Lancaster. The district covered by Lancaster General Hospital includes the seaside resort of Morecambe. PDB is often not apparent until a patient is over 55, and most frequently when they are over 70. The high rates uncovered in the 1970s could well be caused by an environmental factor suffered some 50 to 60 years earlier. This rate for Lancaster was surprising as it had far fewer mills in the 1920s than the other Lancashire mill towns listed and the district had (and still has) lower levels of air pollution than can be found in Preston, which came in second place for PDB and Blackburn and Burnley, all of which suffer from air pollution today.⁴ Even more surprising was the female figure indicated for Lancaster, which was 10.0%. This is by far the highest incidence of PDB ever recorded anywhere and greatly exceeded the figure of 6.5% for men, which is also unexpectedly high. The incidence of PDB quoted in studies is invariably higher for men than for women. No explanation has ever been given for the apparent anomaly in Lancaster, and a combined figure of 8.3% for both sexes has been quoted by some

researchers, often without any mention of the figure of 10.0%.⁵

By 1993, the rates for Lancaster were recorded as 3.7% male and 3.8% female. In comparison, Preston rates were 3.3% and 1.7% respectively in 1993. By 2018, the average rate for PDB in Lancaster was 0.8%.

Prevalence of Paget's disease among hospital patients aged 55 years and over in 31 towns

Town	No of patients	No with disease	Prevalence (%) of Paget's disease		
			Men* (n = 14 444)	Women* (n = 14 610)	Both sexes†
<u>Lancaster</u>	626	58	6.5	10.0	8.3
Preston	1000	82	8.6	6.3	7.5
Bolton	602	42	7.7	6.4	7.1
Wigan	600	42	8.1	5.4	6.8
Burnley	979	74	8.2	4.9	6.5
Blackburn	595	39	8.8	3.8	6.3
Bradford	1000	59	7.9	3.6	5.8
Glasgow	938	50	6.3	4.6	5.4
Leicester	1021	57	7.8	3.1	5.5
Hull	1000	53	7.6	3.1	5.3
Blackpool	949	63	6.5	4.1	5.3
Whitehaven	1002	58	7.1	3.4	5.2
Ipswich	997	50	6.5	3.8	5.1
Southampton	1000	53	6.6	3.6	5.1
Reading	989	56	7.3	2.7	5.0
Bath	998	52	5.3	4.7	5.0
Middlesbrough	734	39	5.9	3.9	4.9
Cardiff	999	41	6.6	3.3	4.9
Macclesfield	890	47	5.3	4.4	4.8
Plymouth	959	48	6.8	2.7	4.7
Portsmouth	999	55	5.4	3.9	4.6
Stoke	1000	40	4.7	4.2	4.5
Oldham	917	45	5.4	3.2	4.3
York	1000	41	5.8	2.5	4.2
Chester	970	43	5.6	2.9	4.2
Warrington	809	37	4.5	3.9	4.2
Birkenhead	994	39	4.4	3.2	3.8
Rochdale	1104	54	4.0	3.1	3.5
Newcastle	1002	32	3.9	2.6	3.2
Carlisle	1482	44	3.9	1.5	2.7
Aberdeen	899	23	2.0	2.6	2.3
All towns	29054	1516	6.2	3.9	5.0

*Age-standardised rates. †Age- and sex-standardised rates.

Figure 1. The six Lancashire mill towns are within the blue box. Strangely, Rochdale, a mill town, is not shown as having a high rate of PDB, but was in Lancashire until 1972, now in Greater Manchester. Lancaster is underlined in red. Chart from "Paget's disease of bone: the Lancashire focus". Br Med J 1980; 280:1105.

In 2002, JH Lever put forward the hypothesis that calcium arsenate pesticide used in USA cotton plantations to combat the boll weevil could have caused the increase in PDB in

Lancashire mill towns.⁶ This pesticide consisted of molasses, water, and calcium arsenate, and crops could be sprayed up to 11 times in a season. However, only up to 60% of the cotton used by Lancashire mills came from the USA in the 1920s and during WW1, in 1918, only 20% came from there, with many other sources including Egypt and India.⁷ Not all of the USA plantations started to use pesticides and then only in any quantity from 1923, so it is probable that less than 30% of imported cotton had been treated. Many farmers were reluctant to use a pesticide because it also killed insects and pollinators. The exported cotton bales were as hard as wood and broken apart in the UK mills using a toothed machine and then passed through a roller in the mixing room. This would have created a great deal of dust and must have been most unpleasant and unhealthy for the few workers involved. However, probably just a small number of mill workers were affected. Only if the cotton was to be dyed would it be bleached and washed.



Figure 2. A bale breaker at Greenbank Mill Pic: Preston Digital Archive

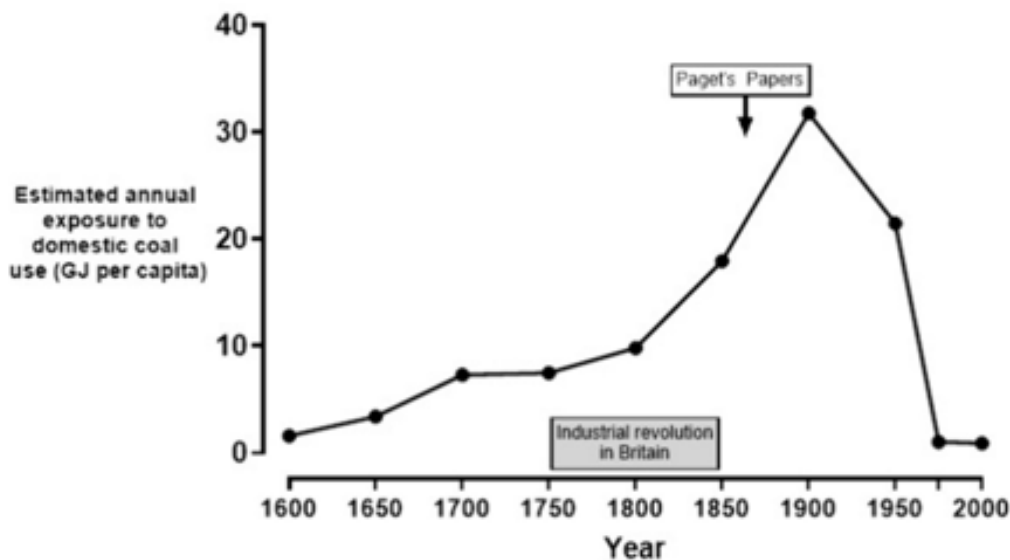
Any wastewater would not end up in the adjacent canal (many mills were next to canals both for transport and water supply). Instead, it would be discharged into streams (many were lined with concrete to improve the flow) or rivers. Heavy metals commonly found in textile effluent include not only any residual arsenic from pesticides but also cadmium, chromium, cobalt, copper, lead, manganese, mercury, nickel, silver, tin, titanium and zinc from dyes.⁸ Any arsenic in the water would be quite dilute and the heavily polluted water

would not be used for irrigation or other purposes. The estuaries on the edge of Preston (Ribble) and Lancaster (Lune) were surrounded by marshland and only reached the western limit of these towns. The argument that waterborne arsenic in tidal estuaries explains the high rates of PDB in Preston and Lancaster has little credibility. Preston once had over 100 operational cotton mills, and by 1927, it still had 60 in operation. In comparison, Lancaster at the same date had five cotton mills, and one producing linoleum, one coconut matting, and two which made baize. There was a small chemical works producing inks and dyes.

A small increase in disease might be expected for those few workers in the mixing rooms. Lever's comments in the same paper on the high levels of PDB in Spain and La Pampa, Argentina, received little attention, unfortunately, as these were significant.

In 2024, Professor Tim Cundy put forward the hypothesis that toxic substances in domestic coal could be a significant environmental factor in causing PDB.⁹ This hypothesis was backed up by a graph indicating the rapid rise and then decline in coal usage which seemed to mirror the incidence of PDB in England and Wales.

From: The Decline of Paget's Disease of Bone and Domestic Coal Use—A Hypothesis



The relationship between estimated exposure to domestic coal burning (gigajoule per capita) in England and Wales from 1600 to 2000. Note the rapid rise during the industrial revolution reaching a peak in the late nineteenth century, around the time Paget first described the disease. There was a rapid fall in the twentieth century as gas and electricity were increasingly used to heat homes and for cooking. Burning coal for domestic purposes was prohibited in Britain in 2023

There appears to be a strong association between the use of coal in England and Wales and PDB, and the deadliest toxic element to be found within coal is arsenic.¹⁰ This review seeks to test the hypothesis that arsenic, from a variety of sources, is the principal environmental factor involved in triggering Paget’s Disease of the Bone. To do this, outliers and anomalies that have been reported, including significant hotspots and medieval cases, will be investigated. In each case, the possible ingestion of arsenic by the local population (differentiating, if possible, between men and women) will be examined. The reason for the high rates of PDB in some countries, but not in others, in the past, will be investigated. Should the association between exposure to arsenic and PDB prove very strong, an explanation as to the reason why will be offered, and predictions made as to the future course of the disease and means to mitigate this. Other toxic elements, which may be a factor when combined with arsenic, will also be discussed.

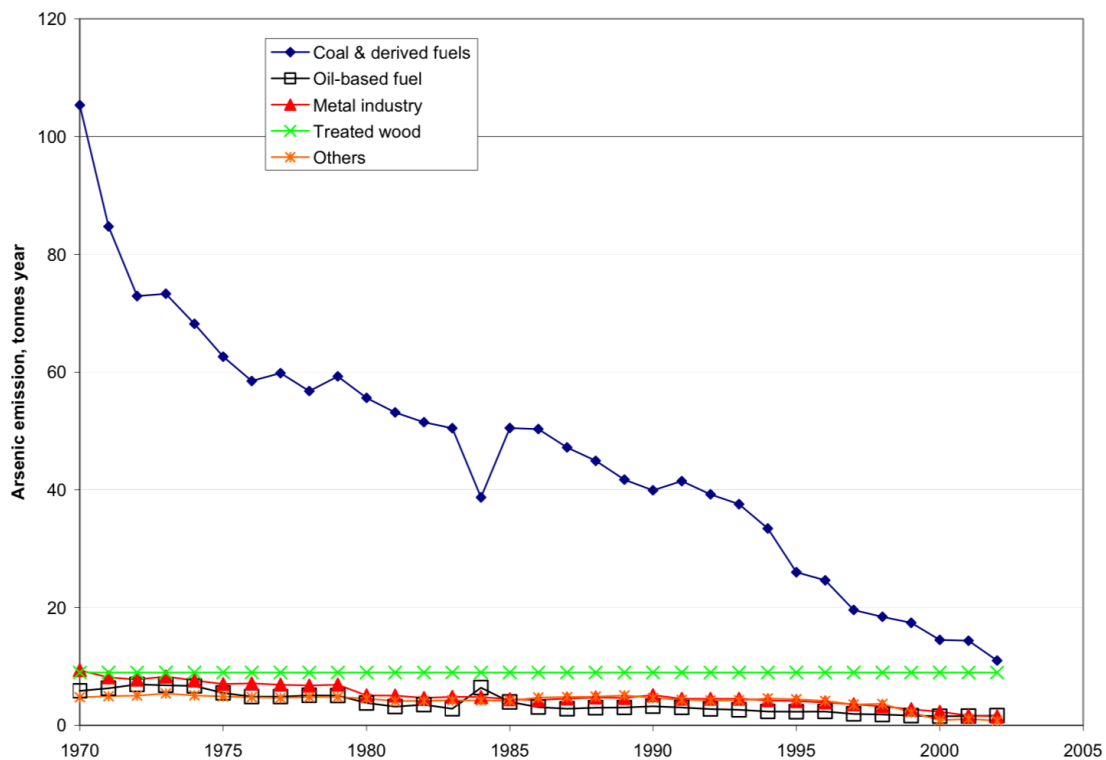


Figure 3. Arsenic emissions in UK from 1970 to 2002 in tonnes/year. No figures were published prior to 1970 but between the clean air act in 1956 and the mid-1970s, the consumption of coal and other solid fuels had been reduced by two-thirds. At this point (1975), the high rate of PDB which had been recorded at that time started to decrease. Coal is by far the most significant producer of arsenic emissions. However, smelting and metal processing facilities would have had a major impact locally. Chart from *Report: Assessment of Heavy Metal Concentrations in the UK*. Reference: AEAT/ENV/R/2013

Methods

Anomalies and outliers can provide clues as to the cause of PDB, particularly on the figures released, which show male and female cases separately. There are several possible sources of arsenic poisoning: airborne particulates, water, and food. This review focuses on airborne particulates and water pollution, but mentions the increasing threat posed by arsenic contamination of certain drinks and foods. As there is thought to be a delay (latency) between being exposed to some environmental triggers and visible signs of disease of perhaps forty or fifty years, this must be considered when investigating possible sources of exposure.¹¹

In the case of the results reported by the team from Southampton General Hospital for UK towns and cities in the 1970s, notable hotspots and outliers will be investigated regarding the industries (separated by sex), likely levels of pollution, topography, climate, health, and diet in the 1920s. The reason for the high levels in the UK will be reviewed by examining the quantity of arsenic in UK coal. In the case of hotspots overseas, local conditions will be examined, such as mines, geology, water supply, pesticides, and fires for cooking and heating. In the more distant past, possible contamination by industrial metalworking processes and water will be investigated.

Town	Male %	Female %	Ratio M/F	Comments
Average	6.2	3.9	1.59	
Aberdeen	2.0	2.6	0.77	Very low figures. Female higher than men.
Carlisle	3.9	1.5	2.60	Low female figures. Surrounded by countryside.
Rochdale	4.0	3.1	1.29	Low figures for a mill town. Low pollution levels.
Plymouth	6.8	2.7	2.52	High male, low female. Dockyard. Arsenic mine.
Reading	7.3	2.7	2.70	High male, low female.
Preston	8.6	6.3	1.37	High male and female rates. Great air pollution.
Lancaster	6.5	10.0	0.65	High female figures., low pollution levels .

Table 1. Anomalies and outliers from “*Paget's disease of bone: the Lancashire focus*”. Br Med J 1980; 280:1105.

The seven significant outliers shown above from the 1980 UK paper will be examined to see if the reported results are in line with expectations should arsenic be the principal trigger. Two locations from the medieval period will be investigated: Norton Priory in Runcorn, Cheshire and St. Peter's, Barton-Under-Humber, Lincolnshire, both these places containing skeletons showing a significant amount of bone disease.

Overseas, the rural areas in the Campania Plain, Italy, have reported a high incidence (2.4%) of PDB. In Spain, the NW Salamanca region, Zamora, the Sierra de la Cabrera region, and Avila have high incidences of the disease (as high as 5.7% in Salamanca). Bordeaux (2.7%) and Rennes (2.4%) are notable examples in France. Further afield, Recife, Brazil and the sparsely populated La Pampa province of Argentina, along with Buenos Aires, have reported a high rate of PDB in South America, whereas the disease is almost unknown in the Andean regions of these countries.¹² In North America, a cluster of historic cases in the Illinois River Valley has been noted, as well as more recent cases in Brooklyn, New York, and in Canada, areas within a 120km radius of Quebec City have been studied.¹³ Unexpectedly, some African American veterans living in states in the southeast of the USA have higher than normal incidences of the disease.¹⁴ New Zealand has a stubbornly high rate of PDB, and although it is decreasing, it may be above the level now experienced in the UK. There are few reported cases in Asia, Andean South America, most areas of Africa (excluding South Africa), and Scandinavia.

Various environmental triggers have been suggested, including a dietary calcium or vitamin D deficiency, dog or other animal ownership, skeletal trauma, and slow viral infections. Repetitive mechanical stress on the bone has been mentioned as a cause. The decreasing incidence of Paget's Disease has sometimes been attributed to widespread measles vaccination.¹⁵ None of these hypotheses can explain all, or even the majority, of the above instances. For the hypothesis that arsenic is the principal environmental trigger of PDB to be shown to be valid, it must be demonstrated that it is associated with an above or below normal rate of PDB in every single one of the examples mentioned above. This requires a local source of arsenic to be identified, with an indication as to why any incidence of PDB is static or decreasing. The long-term impact of arsenic on the human body is linked to cancers of the skin, lung, bladder, liver, and kidney. It is also attributed to an increased risk of heart disease and damage to blood vessels. Where such information is available on these diseases for a particular location, above-average cases of these diseases provide further evidence to corroborate that the local population has been exposed to arsenic.

Case studies

Coal

If arsenic is a principal cause of PDB in the UK, the widespread occurrence in Lancashire rules out arsenic in groundwater as there is no record of this being the case. Many towns and cities were supplied with piped water using a vast number of reservoirs and lakes from peatlands high up in the Pennine Hills which had been constructed during the mid to late Victorian era. Nearly every town had sewage treatment by 1920, albeit sometimes rudimentary by modern standards. The other possibility of arsenic ingestion therefore comes from the burning of coal, both domestic and industrial. However, coal was also widely used as a fuel in Europe until recently and most, but not all, cities there did not report high rates of PDB. What is special about UK coal? A review based on samples from the UK Coal Research Establishment Coal Bank was undertaken in 1999. Twenty-four UK samples from coal fields were analysed for 46 major and trace elements. The samples were representative of the major UK coal fields. Environmentally important trace elements included arsenic, cadmium, lead, molybdenum and selenium. Smaller quantities of other elements were also identified.¹⁶ Fly ash from coal is particularly rich in arsenic. Arsenic can be found in pyrite (FeS_2), forming "arsenian pyrite" where arsenic substitutes for sulphur in the pyrite crystal structure, and can also exist as inclusions of arsenopyrite (FeAsS).

Low-ash coal from Newcastle, England was found to contain 0.8% As_2O_5 (8000 ppm Arsenic Pentoxide). Some buildings in Leeds, Yorkshire, were reported in 1933 to be coated with ash containing 30-230mg/kg of arsenic. Coal from South Wales was also noted for being high in arsenic as was coal from South Yorkshire and the East Midlands which has had levels reported to be as high as 13,000 mg/kg.¹⁷ Lancashire and Cumbrian coal fields frequently had seams containing pyrites, a common contaminant which often contains arsenic. It appears that both the arsenic and lead content of UK coal is in general high, and mostly higher than that found in countries in Western Europe.¹⁸

In comparison, the level found in arsenic-rich bituminous coal in Spain was 83mg/kg, but this was exceptional as it was normally much lower. In Germany, areas with arsenic-enriched coals had 200-400mg/kg although one particular area had a maximum figure of

3,000mg/kg. However, ash from Silesian bituminous coal usually contains 0.05–0.01% As (500–100 ppm).¹⁹

It is the quantity of toxic particulates inhaled by local inhabitants that is important, so it is not only the amount of a toxic material in coal that is significant, but also the amount burned, and the smoke or dust inhaled, the size of particulates being important. The seven UK towns and cities identified as having unusual rates of PDB in the 1970s will now be examined for the prevailing conditions in the 1920s, examining the potential pollution caused by coal and any other possible sources of arsenic.

Other sources of airborne pollutants

Apart from coal smoke, the most significant other source of airborne arsenic affecting the UK population was the smoking habit. There is a wide variation in the arsenic content of different brands of cigarettes. Cigarettes contain far more inorganic arsenic than cigars or pipe tobacco.²⁰ Lead arsenate was widely used in the USA as a pesticide on tobacco plantations, and tobacco plants can also take up arsenic in the soil, concentrating that element in the leaves. Between 1932 and 1957, there was a 200% to 600% increase in As_2O_3 content in American cigarettes.²¹ Smoking was heavily promoted by the major UK tobacco companies in the UK during the 1920s, and as a result, a significant portion of the male population were smokers, with estimates suggesting that around 80% of middle-aged men were regular smokers. Not many women smoked at that time, and so tobacco companies began actively marketing to women. By 1945, 41% of women smoked. Smoking peaked in the UK in 1974, and since then, sales of cigarettes and other tobacco products have declined steadily. Arsenic is methylated and eliminated from the body by urine, but cigarette smoking lowers the methylation capacity of arsenic and hence its elimination from the body.²² The working population in manual jobs and the unemployed had much higher rates of smoking than those with desk-based jobs or in the professions. The highest rates of smoking in the UK were in Northwest England and the Yorkshire and Humber areas.²³ In an article published on 6th January 2016, the Royal College of Physicians declared that the UK “was a world leader in the promotion and consumption of cigarettes throughout much of the 20th century”. The UK figures for 2021 record that 13.1% of men and 10.1% of women smoked, a great reduction from those earlier figures.

There were industrial processes which released arsenic into the air: ferrous and non-ferrous smelting plants, cement works, glass works, particulates from mining activities, burning of industrial waste, pesticide spraying, and natural sources such as forest fires and volcanic eruptions. Occupational exposure could involve handling chemicals with an arsenic content or breathing the contents.

Areas suffering from deprivation frequently contain heavy industrial processes, incinerators and mines; residents and workers there were likely to be exposed to more arsenic for all the above reasons. They were also more likely to be deficient in vitamins and minerals and in poor health, both physical and mental.²⁴ Many such deprived areas in the 1920s and 1930s were in Northwest England, so the increase in PDB in this area is explicable.²⁵ A review of arsenic in ambient air was conducted in the UK and published in 2000. It demonstrated that coal and heating oil were by far the biggest cause of arsenic emissions, although local emissions from ferrous and non-ferrous production processes could be high. The conclusion was that over twenty years of monitoring, arsenic levels in the air had steadily decreased because of pollutant abatement schemes and the switch from traditional coal burning to natural gas.²⁶ This is in line with the rates of PDB which have been steadily decreasing since the 1970s but may now have plateaued.

Water and food

Arsenic in groundwater is an issue when drinking or irrigation water is sourced from wells. The UK towns generally had a piped municipal water supply by 1920, so this would only be an issue in rural areas. Any arsenic in food in the UK would have mostly come from freshwater fish caught in polluted streams, or crops grown on polluted land or sprayed with pesticides. However, fish contain organic arsenic, which is not as toxic as inorganic arsenic.

Seven UK cities and towns outliers

Aberdeen

The rate of PDB for this city was shown in the 1970s to be very low by UK standards (M 2.0%, F 2.6%) and is unusually, slightly lower for men than women. A review for those born in 1921 in Aberdeen shows an increased risk of mortality for men, which could not be explained by the broad range of socio-environmental, mental ability, and health status

variables examined.²⁷ As PDB only becomes apparent in later years, many men would have died prior to PDB becoming apparent. 10% of Scots emigrated between 1921 and 1931, and Aberdeen in particular, had a transient population, with many men moving to cities such as Glasgow to find work. In the first 4 months of 1923, 896 citizens left Aberdeen to emigrate to the USA and Canada.²⁸ The two main industries were fishing (trawling) and working in granite quarries, the other notable industries being paper making, shipbuilding and textiles. Aberdeen has the highest proportion of foreign residents in Scotland, with one in four people born outside the UK. Immigrants arrived from Lithuania, the US, Germany, Ireland, India and France.

Men working at sea or in the granite quarries would not be exposed to particulates containing arsenic during the working day. There is now little heavy industry in Aberdeen and air quality is generally good. The transient population and low life expectancy for men also explains the low rate of recorded PDB, particularly for men.

Carlisle

Carlisle had a high 1970s rate of PDB for men (3.9%) with a much lower rate for women (1.5%). One might have the impression that Carlisle, situated on the edge of the Lake District, would be predominantly rural, but it does have a reasonable amount of industry. During the Great War, the munitions factory at Gretna, some 14 miles distant to the north-west, employed 11,576 women and 5,066 men, some from as far away as Australia. Many of the employees would probably have come from Carlisle. They lived in a specially constructed township and at peak output produced 1,400 tonnes of cordite a week, but the factory was short-lived, closing in August 1919. The textile industry was declining and produced mainly woollen goods and tweeds. Apart from this industry, there was little work in Carlisle for women who may have found employment working on nearby farms. On the other hand, there was plenty of industrial work for men. Such work included railway work (the transport hub employing 20% of the workforce), making tin boxes, foundries, engineering works, printing and working for the John Laing construction company. Two electricity generating stations supplied electricity to Carlisle and the surrounding area: the first power station (1899–1927) was in the centre of the city and the second larger station was at Willow Holme, northwest of the city (1923–1980).

The PDB figures appear consistent with a small city (in population, although large in area) which is not surrounded by any other urban conurbation. By 1994, the rate of PDB had dropped to 1.6% and 0.9% respectively.²⁹ Carlisle has retained some industry, much of it based on industrial estates and is now noted as a centre for transport and logistic companies. Major companies based there are Pirelli Tyres, Nestle, United Biscuits and Northern Foods.³⁰

Rochdale

At first sight, the PDB figures of 4.0% (male) and 3.1% (female) for Rochdale seem remarkably low in comparison to the other Lancashire cotton mill towns. It is, of course, possible that the figures for PDB in the 1970s analysis were incomplete or recorded incorrectly. There were certainly a large number of mills in the Rochdale area in the past, many of them between 2 and 5 miles from the centre of the town. Rochdale is located approximately 450 feet (137 meters) above sea level in the valley of the River Roch, making it relatively high compared to many towns. The winters here are very cold and windy, dispersing the toxic smoke from the area. The town was noted for woollen mills in addition to the ones for cotton. It is impossible to know the levels of pollution in the 1920s, but when a measurement for lead in the atmosphere was undertaken in 1992, the figure for Rochdale was half that for Manchester and less than for Wigan, Bolton, and Bury.³¹ Even so, the relatively low rate of PDB in that town seems difficult to justify without further explanation. One possibility is that there was migration from Rochdale to neighbouring areas such as Manchester in the 1950s as few residents wished to work in the textile mills at that time and there was little other work. The gap was filled by South Asian men who came to Rochdale from the 1950s to the 1980s to work in the textile mills. They settled in the terraced streets near the centre of the town. After the textile mills closed, many of them found jobs in food or taxi businesses.³² Many former residents moved out of Rochdale.

Another factor that would influence the statistics was a change in the boundary of Rochdale in 1974. A new metropolitan borough of Rochdale was formed within Greater Manchester, which covered outlying towns and villages including Heywood, Littleborough, Middleton, and Milnrow. The figures for PDB thus included many previously rural areas not subject to great industrial pollution, and the newly arrived immigrant workers had not been exposed to the earlier pollution, and in any case were

largely Asian and not susceptible to PDB. It was quite usual for the less routine cases to be referred to Manchester Royal Infirmary or North Manchester General Hospital, some 15 miles and 11 miles distant, respectively. This fact alone would account for far fewer cases on record for Rochdale.

Several small specialist manufacturing companies are now based in Rochdale as are transport logistics companies. Both Rochdale and another former mill town, Bolton, have high rates of unemployment approaching 5% and are areas of deprivation.³³ Current rates in Greater Manchester show a PDB prevalence which has increased with increasing deprivation and was, compared to the White population, more common among those who identified as Black or Black British and less common among those who identified as Asian or Asian British.³⁴

Plymouth

A noted naval town throughout much of history, the city's navy base at Devonport (dating from the 1690s) is still the largest in Europe. During WW2, as many as 27,000 people worked in the dockyard. Most of the workers would have been men. During and immediately after WW1, there was also work for men in the nearby Great Consols arsenic and copper mine. At that time, there was plenty of work for women in a multitude of hospitals serving both the city and the many service personnel.³⁵ Many wounded troops were repatriated to Plymouth and treated there. The dockyard area would have been very smoky from the boilers of many ships as well as boilers used to provide heating and power for facilities and the workshop equipment. Some shipbuilding also took place and a 1914 visitor's guide stated "*It is impossible to convey any idea of the varied activities which are to be witnessed at the dock sides and in the many workshops. The visitor should not fail to visit the large Smithery, however much the smoke and soot may drive him to the open air. Here anchors and other heavy metal work are dealt with and the great Nasmyth steam hammer may be seen*". The hospitals and sanatoria with their many nurses and auxiliary staff were situated on higher ground, less susceptible to pollution.³⁶ After WW2, a major cement plant was located in Plymouth, using locally mined limestone which contained arsenic.³⁷ Piles of mining waste still contaminate local rivers and streams.³⁸ The PDB rates of 6.8% and 2.7% M/F are consistent with employment and living conditions in the 1920s and later. In addition to the naval base, Plymouth is now a global centre for marine science and technology.

Reading

Perhaps surprisingly for a town in the Thames Valley in SE England, Reading had, and still has, areas suffering from deprivation and poverty, as well as some more affluent areas. In the 1920s the major industries were the “B”s:

1. **B**rewing, 2. **B**rick and tile making, 3. **B**iscuit making, 4. **B**ulbs and seeds, 5. Transport. Brewing and brick making were male dominated industries and mainly men were employed on the railways. Both men and women were employed in biscuit making, but largely segregated, men undertaking the labour-intensive work. Women were the usual employees for bulbs and seeds, especially during the world wars.³⁹

The largest brewery, Simonds, supplied the British Army. All breweries issued free beer to the workers. In some this was limited to two pints/day, in others it was unlimited. Beer filtration using diatomaceous earth (kieselguhr) can introduce trace amounts of arsenic as can malt kilning. The breweries had their coal-fired boilers and were situated along the River Kennet or the Kennet and Avon canal (in a valley), whilst the railway station and yards were close to the River Thames. The High Street is on a low hill between these two valleys. The brick kilns were close to the River Thames, with the clay being excavated from a hill to the south. The men working in the kilns making bricks, tiles, and flowerpots would have been exposed to great amounts of smoke and coal dust.

Huntley and Palmer had the largest biscuit factory in the world and biscuits were exported throughout the Empire. The factory, which employed over 5,000 people at peak, was in the Thames Valley next to the railway line and had its own railway sidings. The owner of the Huntley and Palmers factory had Victorian ideas about segregating the men from the women employees. Biscuit making involved some heavy manual work, such as stoking boilers and stirring dough and servicing and making machinery in the workshops undertaken by men, with biscuit tin making, cutting and coating biscuits and packing at the other end of the factory allocated to women.

Suttons seeds premises were huge and even had a dedicated fire station along with cottages for the firemen, and stables. They were situated at the end of the High Street on a low hill not far from the gaol, above the smoky valley areas to the north and south. This was an enormous enterprise employing over 2,000 people, mainly women. Many more women worked in the fields and greenhouses around Reading, pollinating plants,

collecting the seeds and bulbs from flowers and plants. Seed production was designated a “reserved occupation vital to the war effort” in December 1915. The demand necessitated that volunteers work night shifts, and extra workers were taken on. Women who were not employed by Suttons or Huntley and Palmer worked in shops (above the valley on a low hill) and in service industries as clerks, teachers and nurses, away from polluted areas.

Reading is a railway town, having a station with many platforms and workshops and goods yards. Situated in the river valley, the areas near these facilities in the steam era would have been enveloped in the smoke produced by the many coal-fired locomotives. Men were clearly exposed to a great deal more pollution than women in Reading in the 1920s, and for some time afterwards. About 64% of the total population would be in work, and women comprised about 20% of that figure. The population of Reading in 1920 was about 90,000. It is the women between the ages of 14 and 21 in the 1920s who would comprise most of the cases of PDB in 1975. The very high rate of PDB for men (7.3%) and the low rate for women (2.7%) can be justified as outlined above. No longer a town with much industry but remaining a transport hub (most rail lines have been electrified), employment now focuses on high-end technology. Fujitsu and Hewlett-Packard both have bases there, and Microsoft and Oracle have established multi-building campuses in the town. Procter & Gamble also has a major innovation centre in the town. The South-Central area of England now has a very low rate of PDB.⁴⁰

Preston

Preston at one time had over 100 cotton mills, but by 1927, just 60 were still operational. Most of the later cotton mills in Preston mills had their own reservoirs to supply water, so they could be situated anywhere, not just next to a watercourse or canal. The area between each mill would be filled with an interminable sea of rapidly constructed terrace houses, later called slums, which would in turn merge with the housing for the next mill or factory with its tall chimneys. It is said that Charles Dickens’ novel, *Hard Times*, was based on life in Preston (called Coketown). With good rail, road, and canal links and a port, Preston also became a magnet for other industries. The demands of the mechanisation of the textile industry led to the growth of engineering skills, and it was these that established themselves there. Joseph Foster & Sons had been formed in 1835 and manufactured heavy industrial plant at its Soho Foundry, including mill engines and

boilers, and some of the largest rotary printing machines. Preston had fifteen firms of millwrights and engineers, four boiler makers, and three other foundries. A major project to provide a full-scale port on the river Ribble, built between 1884 and 1892, provided a site for Dick, Kerr of Kilmarnock to establish their first factory in the town, making locomotives and tramcars.⁴¹

Both men and women would be exposed to toxic smoke, the men in foundries and engineering works more than the women workers in the mills. Preston, in the Ribble Valley, suffers from poor air. In 2023, an analysis revealed 51 neighbourhoods there, covering 59% of the total area, were exposed to air pollution exceeding the World Health Organisation's recommended safety limit, along with Burnley and Blackburn.⁴²



Figures 4 and 5. Life could be rather spartan and bleak for those living in such terrace houses. Each room would have a fireplace.

The UK cotton industry was declining in the 1920s and 1930s, leading to unemployment and poverty in the mill towns. After World War I, an average working-class family bought 26 pounds of bread and 20 pounds of potatoes a week. Fruit and vegetables were luxuries. The local dish, Lancashire hotpot, consisted mainly of potatoes with cheap cuts of lamb. With a poor diet and dire working conditions, the cotton workers were generally in poor health. Many suffered from eosinophilia (18.35%), iron deficiency anemia (28.90%), byssinosis grade 1 (7.80%), dental stains (6.54%), refractive errors (7.80%), chronic bronchitis (4.85%), and upper respiratory tract infection (8.64%). They also had musculoskeletal disorders, asthma and often suffered from hearing loss caused by the noise of machinery.⁴³ Much of the work involved standing or sitting all day.

As for the weather, Preston, like most Lancashire mill towns, has comfortable but largely cloudy summers, but the winters are long, very cold, wet, windy, and mostly cloudy. The cloudy weather, together with air pollution, meant that little UV radiation reached the local populace. As recently as 2019, The Burnley Express (7th March) reported “Thousands of people are being admitted to hospital with vitamin D deficiency at East Lancashire hospitals”. Low levels of vitamin D and poor health make one more susceptible to disease. It is therefore unsurprising that many cases of PDB have been linked to low levels of vitamin D and the consequences, which include low levels of calcium.⁴⁴ Preston had particularly high levels of PDB in the 1970s, with rates of 8.6% and 6.3%, but by 1993, these had reduced to 3.3% and 1.7% respectively.⁴⁵

Lancaster

The figure for PDB reported for Lancaster in 1980 was 58 cases out of 626 patients, giving an overall rate of 8.3%. The male and female numbers are not differentiated, only the percentages. If half the patients were female and half male, this would equate to 20+31 (51 cases). If two-thirds of the hospital patients were female (417 no.), this would give 14+42 (56 cases), so it would appear that was the sort of ratio used in the calculation to arrive at 58 cases. The number of male cases, 6.5%, seems rather high compared with other mill towns, given that Lancaster had far fewer mills and less pollution. Based on this figure, the corresponding number of female cases, using the ratios found elsewhere, would be expected to be in the order of 4.9% (20 cases). This would indicate that some 22 cases should be attributed to the exceptional factors, which raised the level to 10%.

Lancaster is a small, compact city in the northern half of Lancashire, with two close neighbours, the seaside resort of Morecambe and the ferry port of Heysham, which serves Ireland and the Isle of Man. Lancaster had about nine mills, some producing linoleum, coconut matting, sailcloth or baize. There was a workshop making furniture, a small factory making stained glass and a factory, dominating the town with its tall chimney, which made dyes and printing inks. The latter factory of Joseph Storey & Co Ltd. would have used chemical salts for the dyes, which would include salts of copper, cobalt, chromium, cadmium and lead. By 1998, the factory had a workforce of just 18 people making fire retardant and smoke-suppressing chemicals as well as pigment dyes, the low number suggesting that the company was only a minor employer in the area.

Morecambe and Heysham have never had heavy industry, the coastal locations providing an onshore breeze providing good air quality. The water supply for the region came from reservoirs high up in the Pennines.⁴⁶ There was nothing of note to indicate why the PDB rate should be exceptionally high. Although Morecambe did have a cottage hospital, any unusual or major cases would be dealt with by the Royal Lancaster Infirmary.

At the time of the PDB survey in the 1970s, both Lancaster and Morecambe were suffering from a severe economic decline. British industry could no longer compete with that in Germany, India, and the Far East. British seaside resorts in Lancashire, with their unpredictable weather and dated and tired-looking facilities, had been abandoned by the working class in favour of overseas holidays served by low-cost flights. Many of the boarding houses and cheap hotels in Morecambe were filled with retirees, whilst others were converted to care homes. The area was known as “The Costa Geriatrica, where even seagulls don’t bother to land anymore”.⁴⁷ Many of the retirees would have come from other industrial towns in Yorkshire and Lancashire, often having health issues, possibly making the PDB statistics worse than they would otherwise have been. The very high rate of PDB for women alone cannot, however, be explained, even taking this into account, as Morecambe only accounts for a relatively small percentage of the population served by Lancaster Royal Infirmary.⁴⁸

In 1917 the British identified two arsenic-based substances, DA (diphenylchloroarsine) and DM (diphenylaminechloroarsine), which penetrated the German gas masks then in use.⁴⁹ It was thought that these arsenic based weapons would be a game changer,

shortening the war. The substances were packed with a thermite mixture into a small metal cylinder, the weapon being called the 'M' device and deployed in the manner of a grenade. The plan was to build up a sufficient stockpile (200,000 devices) to use on the German trenches in the spring of 1919, with a surprise offensive.⁵⁰

The White Lund site on the outskirts of Morecambe and close to Lancaster was chosen to manufacture this weapon, the previous factory on the site, which had manufactured shells, having spectacularly blown up in 1917, demolishing over 100 buildings and causing 30,000 Morecambe residents to evacuate their homes in panic. The workforce rapidly recruited to make the 'M' device consisted of about 400 "girls", mainly aged between 17 and 21, and about 100 men, to undertake unloading and loading work. The girls were exposed to high levels of arsenic particulates for up to 4 days a week (alternating with 2 days filling, 2 days other work).

Work started in October 1918 and continued after the Armistice until August 1919, with a reduced workforce between April and August 1919. It was the only UK chemical weapon factory to continue production after November 1918. Despite the dangers, the girls did not leave after the war had ended, as Major Tom Davies and factory manager R.A. Stokes looked after them well and took great precautions to ensure their safety in very dangerous conditions. In all, 240,000 'M' devices were manufactured, 50,000 of them sent to North Russia in April 1919 with Major Tom in great secrecy for use against the Bolsheviks. The total amount of arsenic mixture used, which was made by grinding kieselguhr impregnated with liquid DA or DM into fine particles, amounted to about 125 tonnes, this figure excluding the thermite powder and wastage.⁵¹

In 1919, the cotton factories were in decline, and there was little decent work for women on offer in the industrial towns, the returning soldiers needing to find employment and given priority for any work on offer. Meanwhile, the seaside resort of Morecambe was coming alive once more, requiring chambermaids, receptionists, shopworkers, laundrymaids, clerks, etc. The girls had no doubt made good friends during work and most would have stayed in Morecambe after leaving the White Lund filling factory, probably for the rest of their lives.

There were now concerns about the ongoing storage of the potent 'M' device at Morecambe. In June 1920, "The Troubles" were growing worse in Ireland and there were fears that the Irish Republican Army, known in the press as Sinn Féiners, would resort to sabotage in the UK. These fears were not misplaced as a series of arson attacks commenced in November of that year, in Lancashire, performed by gangs of armed men. The removal of the munitions at White Lund had become urgent. The stores were now examined in some detail to decide how to proceed. The results were alarming, as some of the drums of chemicals and weapons were found to be leaking. Some 95 tonnes of arsenic compounds were still left in the unused thermo-generator canisters, and another 128 tonnes were residing in drums and cases.⁵² Any detonation could set off a chain reaction which would cause the evacuation of Lancaster in a westerly breeze, possibly Morecambe as well, causing many deaths among the young and elderly. A clear-up was organised, 50,000 devices being sent to Porton and the rest dumped at sea. No suitable labour could be found to remove the munitions and waste at this time, so this work would have been undertaken by inexperienced men who may have inhaled the leaking contents. There would have been quite a lot of particulates, which would probably have just been left on the ground to blow around in any breeze, giving rise to inhalation of toxic particles by those living in the vicinity.⁵³

It is quite possible that some 20 women, and perhaps 5 or so men, later contracted PDB because of exposure to inorganic arsenic. In the early 1970s they would have been aged in their late 60s to mid-70s. Many retirees from other mill towns had moved to nursing homes in Morecambe. In 1994, a sample of abdominal radiographs of people aged 55 years and over was taken from stored films within the radiology department of the principal general hospital in Lancaster. The radiographs were identified by screening radiographic records over the period 1993–1995. As nine thousand eight hundred and twenty-eight radiographs were studied in the stores covering ten hospitals, this would suggest that many of them had been taken some years previously.⁵⁴ Patients in the earlier survey were not excluded from the later survey. The rate of PDB reported in 1994 was 3.7% of men and 3.8% for women. This compares with 3.3% and 1.7% for Preston. By 2017, the overall rate for Lancaster had reduced to 0.8%. Exposure to toxic elements is particularly dangerous in childhood and adolescence.⁵⁵



Top. Fig 6. View of White Lund filling shed. The tables on the right are for the canisters after being filled and awaiting completion. Note the overhead sprinklers. All photos The National Archives (TNA) WO 142/116 CWO 114.

Bottom. Fig 7. Front and rear view of the fume cupboards. The DA or DM bricks were placed in a box at the back of the first fume cupboard in the line. There were four stages to complete the filling, hence the need for four connected fume cupboards. The filler's hands were inserted into the fume cupboard wearing gloves, taking care with the insulation to prevent gas from escaping. The canister was inserted through an opening in the side of the box.



Fig 8. View of the finishes shed. Tables for finishing – placing the top brock ignitor, friction tape, felt wadding, lid and adhesive. TNA WO 142/116 CWO 114

UK Regions

A paper published in 2021 characterized the incidence of clinically diagnosed Paget’s disease of bone in the UK during 1999–2015 to determine variations in the incidence of the disease by age, sex, geography, and level of deprivation.⁵⁶ It noted the rapid decline in PDB, the figures in 2015 being less than one-third of those in 1999. It also showed that it was more prevalent in areas of deprivation. Although North West England still had the highest rates, these were only marginally higher than the following regions of Yorkshire and the Humber, and then Wales. Yorkshire, Humberside, and South Wales all had, until recently, many coal-fired power stations and steel mills. They also had housing and pollution typical of that found in the North West of England. Surprisingly, South West England came next in order of magnitude. Apart from the city of Bristol, this region has no other city with a population of over 300,000, no coal mines, and little heavy industry. One part of the region has a very distinct identity: Cornwall. This county, together with parts of neighbouring Devon, was extensively mined for the minerals in the ground, many of the mines being opencast. The elements which were mined were largely copper and tin, but the sulphides extracted included iron, lead, silver, zinc, tungsten, manganese, and inevitably, arsenic.

Spoil heaps of abandoned waste now litter certain areas. The groundwater is heavily polluted in places, and dust from the former mines and exposed spoil heaps contaminates the land for miles around. Redruth, Camborne, and Hayle, where many of the abandoned mines were located, are now deprived areas. Local agricultural produce is contaminated with the dust from the former mines and from arsenic-rich streams and well water.⁵⁷ A review published in 2016 demonstrated that 5% of drinking water samples from private wells in Cornwall had arsenic levels above the WHO-recommended limit.⁵⁸

A paper by Daniel Middleton et al [2017] found that 69% of soils in Cornwall exceed the Category 4 Screening Level (C4SL) of 37 mg/kg for arsenic under the “Residential with Homegrown Produce” setting. Category 4 is where the level of risk of cancer is acceptably low.⁵⁹ This means that many of those with gardens, orchards, and allotments are at risk of the effects of arsenic in food. The implications for commercial crops were not addressed..

Cases from medieval times and earlier

Norton Priory

Located in Runcorn, Cheshire, England, it was founded in 1134 as an Augustinian priory and given abbey status in 1391. Medieval skeletons from Norton Priory in Cheshire have revealed that the subjects were affected by an unusual ancient form of PDB disorder.⁶⁰ In some monastic communities, skilled metal workers could cast their bronze bells on site. The bells would be made for abbeys, churches, and monasteries in the region, so this was an important industry. Two bell-making pits have been found, an analysis indicating that the bells were 65% copper, 25% tin. The size of at least one bell was 1m high, 0.8m in diameter.⁶¹ Copper, contaminated with arsenic ores, probably came from Alderley Edge mine (22 miles distant). A wooden shovel recovered in pristine condition from the Alderley Edge copper mine indicated arsenic was present. The arsenic helped to preserve the shovel.⁶² Copper ore is frequently found mixed with arsenic ores, typically arsenopyrite (FeAsS), and also tennantite (Cu₁₂As₄S₁₃) and enargite (Cu₃AsS₄).

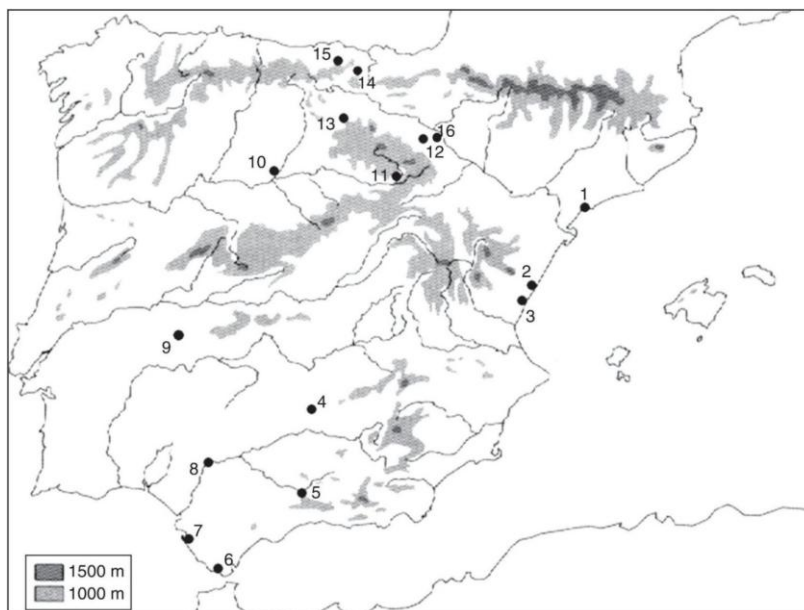
Sandstone for building the priory could be obtained from an outcrop nearby. There were springs on the site providing water from an aquifer in the Wilmslow Sandstone which contains arsenic, released by reductive dissolution of FeAsS.⁶³

St Peter's, Barton-Under-Humber.

Fifteen examples of Paget's Disease have been noted in the churchyard with 2,750 exhumations, the graves dating from AD 670.⁶⁴ This locality was also used extensively for casting bells at various times from the 12th to mid-18th centuries. The copper used for casting bells shows signs of tin and lead contamination, but no tests have been undertaken for arsenic.⁶⁵ As the site is on the Humber estuary, imported ore could have come from many sources.

The Iberian Peninsula

Skeletons showing signs of Paget's Disease have been found throughout Spain, dating from the Roman period up to the 19th century.⁶⁶ The Romans exploited the region for gold, silver, and copper and many new mines were opened, adding to the existing ones being worked. Clusters of diseased skeletons were found close to Valencia (no. 3), Clunia (no. 11 on map, named San Martin de Castillo), and Palencia (no. 13 on map, named San Juan de la Hoz) near where there were mines. In Clunia, there were thermal baths, and such water often contains high levels of arsenic derived from arsenite.



- | | | |
|---------------|-------------------------------|------------------------------------|
| 1.- Tarragona | 6.- Baelo claudia | 11.- San Martín del Castillo |
| 2.- Paterna | 7.- Cádiz | 12.- La Rioja (indeterminate site) |
| 3.- Valencia | 8.- Sevilla | 13.- San Juan de la Hoz |
| 4.- Jaén | 9.- Torre de Palma (Portugal) | 14.- San Andrés de Astigarribia |
| 5.- Granada | 10.- Valladolid | 15.- Santo Tomás de Mendraka |
| | | 16.- Santa María la Vieja |

Figure 9. Cases in which there is paleopathological evidence of Paget's disease of bone in the Iberian Peninsula. *Paget's Disease of Bone: Approach to Its Historical Origins* Reumatol Clin. 2017;13:66-72 Pages 63-124 (March - April 2017)

Notable levels of PDB from outside the UK

Campania, Italy

The Campania Plain contains active volcanoes such as Mt Vesuvius, Campi Flegrei (Phlegraean Fields), and Ischia. The soils of Campania region show higher median concentration levels of arsenic and other heavy metals than in other Italian and European areas.⁶⁷ In addition, all these exceed the intervention limit set by Italian legislation and rural communities use well water. Assessed arsenic levels in water from various areas were generally found to be within legal limits except for Canello Arnone, Mondragone, and Sessa Aurunca sites, where there were high concentrations of 145.3 $\mu\text{g/L}^{-1}$, 102.5 $\mu\text{g/L}^{-1}$, and 25.4 $\mu\text{g/L}^{-1}$, respectively. The region also has a high level of air pollution caused by the burning of toxic waste.⁶⁸ An increased PDB clinical severity was observed in the PDB cohort from Campania in comparison with patients from other Italian regions. A gene that appears to be implicated is the zinc finger gene, ZNF687. The rate of PDB, at 2.4%, has remained unchanged and has not reduced in line with the figures in the UK.⁶⁹ Current levels of skin, lung, and bladder cancer, all of which can be caused by arsenic, are above those for other areas in Italy.⁷⁰

N W Salamanca, Spain.

Arsenic has been found in a large number of water, rock, soil and stream sediment samples from around an area of former mining activity in Salamanca province, Spain. In some relatively abundant granitic and metamorphic zones, hydrothermally altered, the arsenic contents are high, contaminating the soil and water.⁷¹ Soils situated near the mine spoils contain extreme levels of arsenic (>1000 mg/kg). N W Salamanca, along with other areas of Spain, has many abandoned Roman gold mines. The soils in the Province of Salamanca, Spain, have recorded a total arsenic concentration that varied from 5.5mg/kg to 150mg/kg, and water-soluble arsenic ranged from 0.004mg/kg to 0.107mg/kg, often exceeding the guideline limits for agricultural soil. The rate of PDB has been reported as being 5.7%.⁷²

There is a mining area one kilometer west of Losacio village in the northwest of the Zamora province, where the former Clara mine is located. The study of an agricultural field impacted by the former exploitation of an arsenical lead-antimony deposit has revealed the presence of high pollution levels. The soil total concentrations of Sb, As, and

Pb in the uppermost soil layer (14.1–324, 246–758, and 757–10,660 mg kg⁻¹, respectively) greatly exceed the maximum tolerable levels in agricultural soils.⁷³

Sierra de la Cabrera, Madrid Province, Spain.

According to Recio Vazquez et al. (2011), there is a potential risk for the catchment area of the Madrid Detrital Aquifer (Spain) of being contaminated by arsenic.⁷⁴ Although the area does not have many mines, there is an abandoned smelting factory, and water is also contaminated by hydrothermal vents with sulfides containing arsenopyrite. The area is a focal point for PDB.⁷⁵

Avila, Spain.

This area has been identified as a hotspot for PDB.⁷⁶ There are high levels of arsenic in the groundwater in the area.⁷⁷

Spain, in general, has extremely high rates of lung and bladder cancer.⁷⁸ It also has an increasingly high rate of skin cancer.⁷⁹ Salamanca has a high rate of colorectal cancer, possibly attributable to heavy metal ingestion.⁸⁰ Illegal cigarettes, which contain excessive levels of arsenic, are widely available in Spain.

Bordeaux, Rennes, and Nancy, France

A paper in 1982 identified PDB rates in some European towns, quoting Bordeaux 2.7%, Rennes 2.4%, and Nancy 2.0%. The survey consisted of a postal questionnaire to radiologists in 11 countries, and radiological surveys among hospital patients aged 55 and over in 15 towns. 1,416 replies from radiologists indicated that the disease was most frequently seen in Britain, followed by France, but was lower elsewhere. The rates in three French towns, all with extensive vineyards, were not dissimilar to rates in some UK towns at that time.⁸¹ Sodium arsenite (NaAsO₂) was used as a spray to control grapevine trunk diseases in French vineyards until it was banned in 2001. In addition, Bordeaux mixture, in combination with arsenical sprays containing calcium arsenate and lead arsenate, was used against the grapevine moth until 1971.

Lung cancer rates in Bordeaux, France, are a subject of ongoing investigation due to concerns about potential links to vineyard spraying and other factors. A study in the

National Institutes of Health (NIH) indicated a significantly higher risk of lung cancer among vineyard sprayers, particularly non-smokers, compared to a control group

Hungary.

The Great Hungarian Plain, which covers most of that country, has high levels of naturally occurring arsenic and is the most severely affected region in Europe.⁸² Whilst major cities such as Budapest would have had water supplies within EU limits for arsenic, there were many regions that did not comply. Whilst comprehensive data for all regions is not available, the two Hungarian towns with PDB data show a higher incidence of PDB than six other European towns in 2000-2001.⁸³

Recife, Brazil.

The frequency of PDB in South America is generally very low, but there are a few notable exceptions. One of these is Recife, Brazil, which has a relatively high number of people of European descent.⁸⁴ At a local osteoporosis center, a total of 7,752 patients were assessed, of which 53 presented with PDB, making the prevalence and incidence rates comparable to those from Southern Europe.⁸⁵ The water supply in the Metropolitan Region of Recife is quite complex, consisting of a series of integrated systems and complementary isolated systems. Main surface waters include the basins of Tapacurá and the Gurjaú and Botofogo dams, as well as rivers Capibaribe, Ipojuca, Beberibe, among others. Industrial wastewater is discharged into waterways without prior treatment, which has made the rivers unsafe sources of potable water, thereby forcing the city to procure water from distant basins or wells. Soils and rocks of Pernambuco State, where Recife is situated, have a high concentration of arsenic in their composition.⁸⁶

La Pampa, Argentina.

La Pampa is a sparsely populated province of Argentina, located in the pampas in the center of the country. Arsenic concentrations in groundwater samples from La Pampa range from less than 4 to 5300 µg/L. Rural areas are not protected by drinking water treatment. 95% of groundwater samples exceed the WHO guideline of 10 µg/L and 73% of groundwater samples exceed the Argentine national standard of 50 µg/L.⁸⁷ This area of Argentina has a high proportion of residents of Italian extraction, some of them skilled ranch hands known as “Gauchos”. Ninety-five percent of Paget patients there were of European descent, and five percent were non-European, while in the control group, the

proportion of European descendants was lower.⁸⁸ No doubt, many patients were treated in Buenos Aires, with a high rate also being recorded there. Residents of Andean heritage do not appear to be affected, having adapted to an environment with high levels of arsenic.⁸⁹

High levels of skin, bladder, and digestive tract cancers are to be found in the La Pampa area.⁹⁰

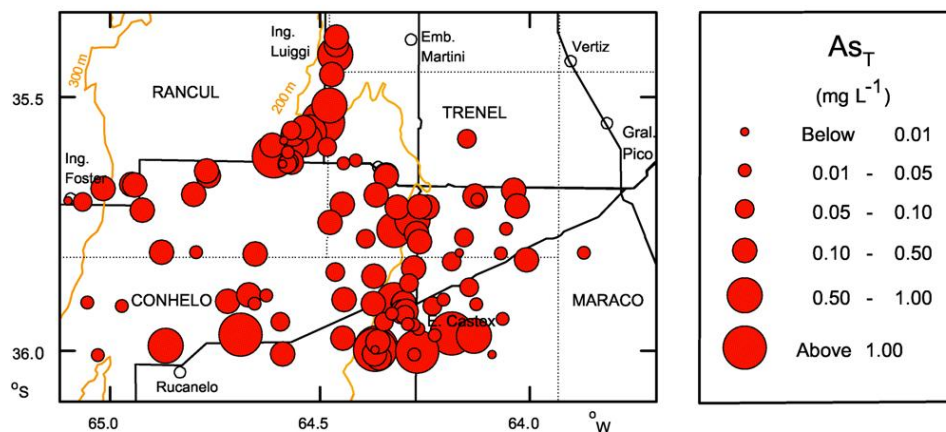


Figure 10. Distribution of total arsenic (As_T) in shallow groundwaters from the loess aquifer of La Pampa. *Arsenic in groundwater in La Pampa Province, Argentina.* British Geological Survey.

Illinois River Valley, USA.

Five cases of presumed PDB in prehistoric American-Indian skeletons in several locations in the Illinois River Valley were published by Denninger in 1933.⁹¹ There were, of course, no Europeans in prehistory. The locations of the archaeological sites varied from Quincy in the southwest to Jolie in the northeast. The aquifers in the valley basin are known to have high amounts of arsenic.⁹²

New York, Pennsylvania, Atlanta, and Lexington, USA.

A study by Guyer et al in 1980 using over 1000 pelvic X-rays in each case showed an incidence of PDB of 3.9% in Brooklyn, NY, but only 0.9% in Atlanta, GA. Another study by Lluberas-Acosta in 1986 using 333 bone scans indicated a rate of 2.1% in Philadelphia, PA, and a study by Rosenbaum in 1969 with 1000 pelvic X-rays found not a single case

in Lexington, KY. The northeast of the USA had much higher rates of PDB than elsewhere.⁹³

In the winter of 1926, New York suffered from severe soot-laden smog caused by homes and businesses burning soft coal which produced far more smoke than the hard variety (which was in short supply).⁹⁴ Pollution levels in New York did not improve until 1965, the Brooklyn area in particular having many industries.⁹⁵

Atlanta had the large Fulton Bag and Cotton Mill, but nowhere near the number of cotton mills located in many Lancashire towns in England. The other industry of note, then and now, was the manufacture of Coca-Cola. Atlanta became a centre for aviation and developed a thriving commercial district. Georgia did have major power stations fuelled by coal, but these were not close to large urban populations. Most electricity was generated by hydro power. Atlanta has a few very cold days (relative to some other southern states) in winter, which are otherwise mostly quite mild. Pollution caused by domestic coal burning would be far less than in the states in the northeast.⁹⁶

Philadelphia is the sixth-most populous city in the United States. The city is the urban core of the larger Delaware Valley, also known as the Philadelphia metropolitan area, the nation's eighth-largest metropolitan area. By 1950, Philadelphia contained two-thirds of the area's industry, the majority in chemicals, metals, paper products, petroleum refining, and plastics. Pollution of all types, including air pollution, was particularly bad in Philadelphia until the 1970s.⁹⁷

Lexington is known as the "Horse Capital of the World" due to the hundreds of horse farms in the region, as well as the Kentucky Horse Park, The Red Mile and Keeneland racecourses. It has significant medical research and hospital facilities, and the university is the largest employer in the city. While predominantly "White", the percentage of the White population has decreased over time. The city has become increasingly diverse, with a growing number of Asian residents, primarily from China and India. The summers are warm and humid; the winters are short, a few days are very cold, and wet, and it is partly cloudy year-round. Over the year, the temperature typically varies from minus 3°C to 30°C and is rarely below -13°C or above 33°C. Over 90% of electricity generation was produced by coal-fired power stations in the 20th century. The nearest coal-fired power

station was located 15 miles west of Lexington. Lexington-Fayette has better air quality than 72% of cities in Kentucky.⁹⁸

It is of interest to note that a review submitted in December 1979 showed that in New York, more White patients had PDB (3.9%) than Black ones (2.6%), whereas in Atlanta, only 0.9% of White patients had PDB but 1.2% of Black ones did, there being much higher rates for males. As the disease is little known in Africa, this would strongly suggest that an environmental factor, rather than a genetic one, influenced these figures.⁹⁹

The PDB levels found in these studies are in line with those which might be expected given the industry and power stations in these areas, the population density, the climate, and the amount of domestic coal burning.

Quebec Province, health regions: Capitale-Nationale, Mauricie et Centre-Du-Québec, and Chaudière-Appalaches, Canada.

The above regions, which straddle the St Lawrence River, have been closely studied since the year 2000 and show above-average incidences of PDB for Canada.¹⁰⁰ No notable mines are producing any toxic minerals in the immediate area. However, there is at least one paper and pulp mill in the vicinity. It has been suggested that those affected, of French extraction, may have inhaled smoke from fires or suffered from cadmium poisoning. Wood-burning stoves are a common source of pollution in the area.¹⁰¹ From the 1970s until the end of 2003, timber was treated with Chromated Copper Arsenate (CCA), a wood preservative that was widely used to protect wood from decay and insect damage. After this date, existing structures built from CCA-treated wood were allowed to remain, and CCA is still available to treat wood for industrial uses. Burning CCA-treated timber releases toxic substances, including arsenic and chromium, into the atmosphere through smoke and ash. There were arsenic particulates in the smoke, and the ash could contaminate soil and water if spread on land. Whilst residents were warned not to burn treated timber, this advice was sometimes ignored.¹⁰² Disposal of treated timber, if not sent to designated tips or incinerators, resulted in the chemicals leaching out.

One of the reasons for the flouting of the regulations was that it was often difficult to determine if the timber had been treated. Initially tinted green, the wood subsequently turned grey, looking somewhat like untreated wood.¹⁰³ It could also be incorporated into

plywood or chipboard, or painted or varnished, covering up the treatment. Freshly treated timber, which had not been allowed sufficient time for fixation, if handled without gloves, could cover the skin with CCA. It was used for children's climbing frames and decking, exposing children to the toxic chemicals during play. Sawing the timber produces dust containing arsenical particulates.

Other possible sources of arsenic and another toxic metal, cadmium, were the smoking of Canadian tobacco in cigarettes, which contain high levels of cadmium.¹⁰⁴ Counterfeit cigarettes can be particularly high in arsenic.¹⁰⁵ Arsenic is found naturally in the timber and plants used to make paper and pulp. The effluent and deinking sludge from such plants, located along the St Lawrence River, often contained arsenic and cadmium. PDB in Canada has declined in recent years, as has been the case in the UK.¹⁰⁶ The dangers of CCA-treated timber in Canada were first identified in the early 1990s by Health Canada studies. Before that, few precautions were taken. Quebec is among the Canadian provinces with the highest rates of lung cancer, both in terms of incidence and mortality. In 2015, Quebec had the highest incidence rate of bladder cancer among all Canadian provinces, according to research published on ScienceDirect.

Rheumatologist and researcher at the University of Laval in Quebec, Dr. Laëticia Michou, has speculated that a component of wood smoke from wood-fired heating, such as heavy metals, may be an environmental factor in Paget's Disease.¹⁰⁷

SE USA States veterans (African Americans).

A cluster of PDB cases has been found amongst veterans whose records were held in the Birmingham VA Medical Center (BVAMC) in Alabama, between January 2000 and December 2020.¹⁰⁸ The figures for Black veterans were higher than those who were White veterans, although both were unexpectedly high. The Black troops served in combat roles in Vietnam at a higher rate than their representation in the US population.¹⁰⁹ Only 5% of officers were Black, and most were foot soldiers. This meant they were often closer to the areas where herbicides were sprayed and were more likely to be exposed. In 1965, African Americans made up 31% of ground combat battalions in Vietnam. The most notorious herbicide was Agent Orange, but what is less well known is that a variety of herbicides were used by the USA in Operation Ranch Hand during the war. These were identified and shipped using colour-coded bands on 55-gallon drums, with the names

derived from the colour of the band. The most widely used herbicides were Agent Orange (orange band) and Agent White (white band), followed by Agent Blue, Agent Purple, Agent Pink, and Agent Green.

The Agent Blue herbicide contained 26.4% sodium cacodylate and 4.7% cacodylic acid in water. Cacodylic acid ($C_2H_2AsO_2$) is a highly soluble organic arsenic compound that is readily broken down in soil. According to military herbicide records, more than 1.1 million gallons of Agent Blue were dispensed between 1962 and 1971.¹¹⁰ Approximately one-half of all Agent Blue was used for crop destruction missions; it was the agent of choice for the destruction of rice crops. It was employed in situations requiring rapid defoliation, causing noticeable browning or discoloration in one day, with maximum desiccation and leaf fall occurring within two to four weeks (Darrow et al., 1969). The remainder was used in defoliation or sprayed around base perimeters, being delivered by helicopters or ground vehicles with sprayers attached to them (Young et al., 1978). The normal altitude of the aircraft for spray application was 150 feet, flying at a speed of 130 to 150 knots, and producing a swathe width of 240 m per aircraft. There was considerable drift of the spray. A subsequent review found that the life expectancies of animals exposed to Agent Blue were reduced to less than ten percent of the unexposed animal population.¹¹¹ The human liver absorbs 40 % of cacodylic acid on exposure, and military personnel with prolonged exposure had breath smelling of garlic.

285 individuals were identified with the disease, the cluster of African American patients presenting at a younger age than their peers' age at diagnosis: 64.6 vs.70.1 years. However, they did not have higher alkaline phosphatase levels, a higher proportion of polyostotic disease, or symptoms and complications. US military veterans are 25% more likely to be diagnosed with lung cancer, compared to the general population.¹¹² High levels of bladder cancer have been reported amongst veterans, attributed to the rainbow group of defoliant and herbicides used in Vietnam.¹¹³



Figure 11. A UH-1D helicopter from the 336th Aviation Company sprays a defoliation agent over farmland in the Mekong Delta. (U.S. Army/Spc. Brian K. Grigsby)

The Vietnamese had a life expectancy of 72.91 years in the year 2000, versus one of 77.74 in the UK at that date. Almost half of the women and just over one-third of men aged 50 years and older in Vietnam meet the US National Osteoporosis Foundation criteria for osteoporosis treatment, and some cases of PDB may have been diagnosed as such.¹¹⁴ There is little doubt that Asians in general are not susceptible to PDB, but that disease is also under-reported and infrequently recognised in countries such as Vietnam.¹¹⁵ Radiology centres are lacking in rural areas of Vietnam, so many cases of PDB would go unreported.¹¹⁶ The very high rates of lung and bladder cancer, particularly among men, would mean that death would occur from one of these diseases before PDB becomes apparent.¹¹⁷ The incidence of PDB would only be raised in the area where Agent Blue was used: the Mekong Delta, regions along the central coast, and the Ho Chi Minh Trail areas.

New Zealand.

Along with most Western countries, the prevalence rate and severity of PDB have declined in New Zealand, indicating a rate of 2.6% in 2005-2006 from a survey in Auckland of those of European descent. The rate in New Zealand is thought by this

researcher to be higher than in the UK, although this is disputed by Auckland University professor Tim Cundy.¹¹⁸ There appears to be no one area far more prone to the disease than any other, with high rates in both the North and South Islands. “New Zealand is different” is a claim often made by New Zealanders. Being so distant from other countries has forced New Zealanders to be largely self-sufficient. Timber is a very important resource, featuring both native and exotic species, with pine being the most dominant. About 90% of plantation forests are radiata pine (*Pinus radiata*).

Many older houses have been constructed of timber with little, if any, insulation. With no nationwide network of gas pipelines, heating was previously mainly provided by wood or coal fires, but more recently by electricity. As well as the use in house structures and cladding, pine is also used to make plywood and MDF, decking, playground structures, vineyard posts and trellising structures, outdoor furniture, fences, pallets and crates, pulpwood and newsprint.

The New Zealand climate results in prolonged exposure to rain and humidity, as well as insects and fungi, which threaten the structural integrity of softwood, so timber treatment is essential to ensure its longevity. The most common treatment for wood used in external applications is CCA, a mixture of chrome, copper, and arsenate, these elements combined in a water-based mixture which is infused into the timber under pressure. With CCA treatment, wood can last for 40 years, and often much longer, even when it is exposed to the weather or a harsh estuarine or marine environment, and/or is in direct contact with the ground or with fresh or salt water

Most countries have prohibited the use of CCA since the early 2000s because of the inherent dangers caused by the arsenic. The New Zealand timber industry has commissioned several studies that claim that there is no significant risk. Although advisory notices were issued against burning treated timber in fires, sawing the timber, or using wood ash in gardens, these notices were, and still are to a lesser extent, widely ignored.¹¹⁹ A 2019 study carried out for the Nelson District Council found air quality in the Nelson South area detected high levels of arsenic in the atmosphere, concluding that arsenic was strongly associated with the solid fuel burning considered to be from the use of copper chrome arsenate (CCA)-treated timber as fuel for domestic fires.¹²⁰ However, although many North Island homes are now heated by electricity, one-third still had

wood-burning fires to heat them in 2018. Whilst arsenic is present at high levels in some rivers, arsenic in drinking water is closely monitored and is unlikely to be at a level sufficient to cause PDB.¹²¹ The rate and severity of PDB are declining, but are not greatly different from the UK population with similar genes.¹²² A review of vineyards and kiwi fruit orchards which frequently use treated support posts concluded in 2018: “New Zealand research and contaminated site investigations identify arsenic in soil within 400 mm of posts at concentration well above both soil guideline values for long term human health protection and levels which may result in a health response in children. Although these ‘hotspot halos’ are small, they are numerous and highly elevated; and many hotspots may be included within the exposure area of a residential backyard.”¹²³

New Zealand has a high rate of bladder cancer, 39.8/100,000, which compares to a rate of about 16/100,000 in UK.¹²⁴ Skin cancer is among the highest in the world. There is some uncertainty as to whether arsenic can cause melanoma as well as other types of skin cancer. The latest research suggests that arsenic can cause melanoma.¹²⁵

Scandinavia.

Very few cases of PDB have been recorded here. This assertion is based on postal survey questionnaires sent out by a team from Southampton University to European radiologists over 40 years ago. A report published in 1982 stated that there was a 27% response rate, most in Scandinavia coming from Norway and in particular Oslo, with a notable one in Sweden from Malmö with a 0.4% incidence of PDB (there were just five recorded cases there).¹²⁶ Whilst the rate was, and may still be, very low in these few locations, it is a somewhat sweeping assumption to conclude that it is very low everywhere in Scandinavia based on such limited data and low numbers. There were considerable variations between towns and cities in the UK, Italy, and Spain, so the same could apply in Norway and especially Sweden, with its heavy industry in the centre of the country and mines in the north, locations which did not submit data.

Most people of Anglo-Saxon heritage have some Danish genes, the word “Danish” referring to the Kingdom of Denmark. One well-known king, Harald Bluetooth, ruled from 958 to around 986 AD. The kingdom at that time included Norway and the most southerly areas of Sweden (Skania and Blekinge) where Malmö is situated. While estimates vary, some studies suggest that up to 6% of the English population may have

Viking DNA. Scottish and Irish populations, especially in areas such as the Shetland and Orkney Islands, have shown even higher percentages, with some estimates reaching 16%. Populations from all areas of Britain and Ireland were found to have 3–4% Norwegian Viking ancestry.¹²⁷ It would seem unlikely that the genetic makeup of the British of Anglo-Saxon descent would be so different from the Scandinavians as to cause far greater cases of PDB in the UK, by a factor of 10 or more. The Sámi people, who are an indigenous group, inhabit the northern parts of Sweden, Norway, Finland, and Russia. These people would have a different genetic makeup from other Scandinavians but have not been included in any statistics for PDB.

Most power in both Norway and Sweden is generated by hydroelectricity. There are no coal mines in Norway (other than in the very remote island of Svalbard) and only a few in Sweden, which needed to import most of its coal, mainly restricted to high-quality coal from the UK, which had few impurities.¹²⁸ This coal served ships, steam trains, and some of the heating stoves in urban areas. The rural areas, along with the remaining urban areas, used wood for fuel, which was plentiful. During both world wars, the import of coal was disrupted, and the use of wood as a fuel doubled. Domestic heating was largely provided by stoves that had a combustion chamber with a door, which was closed during operation. Although more than one stove could be provided in a house, it was usual to just light one stove, which would spread heat throughout the house. Inhabitants would therefore not be exposed to smoke particles whilst in the house. This type of wood stove is still in use today. Swedish houses are very well insulated.

Initially relying on natural resources (timber and mining), Sweden later developed engineering and the pulp and paper, steel, and chemical industries in the 20th century. Norway is rich in natural resources with relatively little industry. Tourism, mining, fishing, and farming provide employment in coastal and rural areas, and services, finance, insurance, and real estate in urban areas. Nowadays, there is a thriving offshore industry.

With low-density towns and cities and much reduced coal burning compared to some other northern European cities, exposure to arsenic in Scandinavia was limited, with one notable exception. Some of the copper and iron ore mines in northern Sweden had ores that contained large amounts of arsenic. This piled up in tailings and was sold at rock-bottom prices (excuse the pun). However, most emissions of arsenic came from copper

smelters, where cases of lung cancer were found to be well above normal.¹²⁹ It is quite possible that, because of the very high levels of arsenic in the air, those affected by emissions from smelters succumbed to cancer caused by arsenic before any latent PDB had been diagnosed.¹³⁰ The steel industry, based in central Sweden, used coke, coal, and electricity.

Unless, or until, rates of PDB in those few areas subject to high arsenic emissions can be reviewed, it is not possible to conclude that the rate of PDB in Scandinavia is low everywhere. Some researchers have implied that there is a low rate, primarily as a result of the genetic makeup of the population there.¹³¹ The issue of smoking will be covered later, as this could be very significant, as many Swedes chew snus instead of smoking.¹³²

Non-Western populations.

It is also thought that South Asians are less susceptible to PDB, according to an article on the incidence of PDB among different ethnic groups.¹³³ However, the same article (Mira Merashli and Ali Jawad, 2015) also states, “However, it is very likely that this disease is under-reported in these populations, especially given the lack of prevalence studies in Asian and African countries.” Another UK study published in 2023 stated, “Within Greater Manchester, it was more common in those identifying as Black or Black British and less common in those identifying as Asian or Asian British.”¹³⁴ A New Zealand paper in 2012 concluded “...that an environmental determinant to the disease exists and that Asians are not genetically protected.”¹³⁵ The cases of PDB in India have increased recently, with a preponderance in the south of the country.¹³⁶ The southern state of Tamil Nadu has a notably high number of cases, and the emissions from thermal power plants are particularly bad, no flue gas controls being fitted to coal-fired power plants there.¹³⁷

If Asians are less susceptible to PDB, there are various possible explanations. The wave of Asian immigrants to the UK started in the 1950s and 1960s, with a further wave in 1972 following the expulsion of Asians from Uganda. These immigrants had generally escaped the toxic smoke encountered by Britons earlier in their lives. They also tended to drink and smoke less than those of Anglo-Saxon heritage, especially if Muslim. Drinking and smoking decrease arsenic methylation.¹³⁸ In the USA, the Centers for Disease Control and Prevention (CDC) in 2016 found that Asians have considerably higher biomarker levels of cadmium, lead, mercury, and arsenic than Whites, Blacks, Mexican

Americans, and other Hispanics in the United States.¹³⁹ It is therefore likely that many Asians have a better methylation ability than Europeans. Asians control melatonin differently than Europeans, particularly at night. Melatonin is a strange compound, being found to alleviate arsenite toxicity.¹⁴⁰ It is linked to autophagy in aging-related neurodegenerative diseases.¹⁴¹ African Americans were found to have high levels of melatonin, and women have higher levels than men. The Chinese have traditionally consumed large quantities of medical herbs containing melatonin.¹⁴² In Japan, melatonin is widely prescribed for children.¹⁴³

Indian life Expectancy from 1901 to 2022

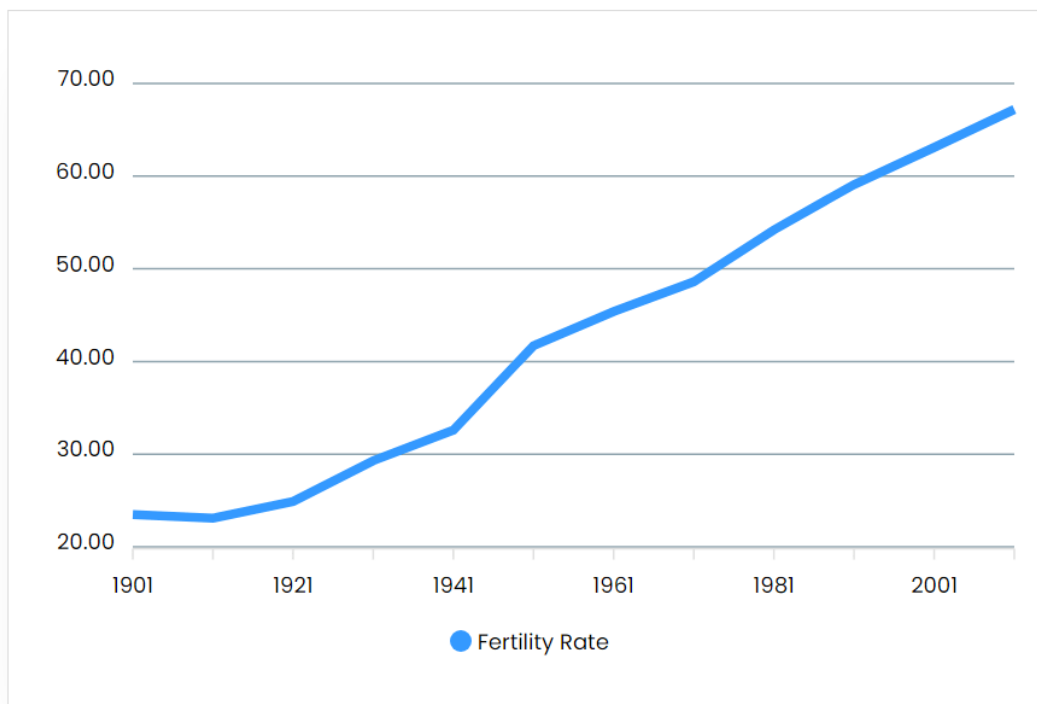


Figure 12. Indian life expectancy 1901-2022. In Pakistan in 2024, life expectancy at birth was 70.30 years, but in Japan it was over 84 years. This chart indicates that few cases of PDB would be likely in the Indian sub-continent prior to 2022. FactoData.

Other possibilities are a failure to diagnose PDB in many Asian countries owing to basic medical facilities, a lack of knowledge by medical practitioners, and perhaps, most importantly, a reduced lifespan. PDB is often undetectable until a person is at least 70 and often over 80 years old. Methylation of arsenic decreases after the age of 50.¹⁴⁴ Many South Asian countries had a low life expectancy until quite recently. Pollutants, such as arsenic, cause high rates of lung cancer in South East Asia, which may prove fatal before

PDB is diagnosed.¹⁴⁵ This would help to explain the results of limited studies.¹⁴⁶ Skeletal abnormalities may not be attributed to PDB but incorrectly to fluorosis.¹⁴⁷ Chinese coal thought to have high levels of fluorine had high levels of arsenic in reality.¹⁴⁸

On the other hand, Japan has a high life expectancy and very low rates of PDB. Some power stations still burn coal, and Japan's coal supply is almost entirely sourced from imports, as domestic coal production ended in 2002. The main source of coal is Australia, which produces coal with a very low arsenic content.¹⁴⁹ Japan claims it only uses “clean coal,” which is a term to describe a collection of technologies used to make existing coal-fired power plants less harmful to the environment. Average dietary arsenic exposure is higher in Japan than that reported in other countries, partly because of the common use of edible seaweed.¹⁵⁰ However, the Japanese appear to tolerate the arsenic in that seaweed without major adverse effects. It was reported that the population who consumed this seaweed (typically just once or twice a month) had low rates of smoking and drinking, which may be significant. Seaweeds are rich in minerals and dietary fibre, and dietary seaweeds have been reported to have antioxidant and antimutagenic effects in experimental studies.¹⁵¹ If the hijiki seaweed is soaked with water, boiled, and the water discarded, as is standard practice, most arsenic will be removed. Some differences exist concerning the clinical features of PDB between Japanese patients and patients from high-prevalence countries.¹⁵² The Japanese are predominantly descended from the Yayoi and Kofun people, who migrated to Japan from the Korean peninsula during the 1st millennium BC. It may be that they and Koreans have built up a degree of tolerance of arsenic in that time, as have the Andean Indians. Evidence has been found that humans can adapt to arsenic, having an increase in the protective variants of the AS3MT gene.¹⁵³ Whilst one study concentrated on Andean Argentinians, another investigated Indians of Aymara-Quechua and Uru ethnicities from Bolivia. This latter study suggested that arsenic exposure has been a driver for human adaptation to tolerate arsenic through more efficient arsenic detoxification and that this adaptation is prevalent throughout the Andean Indian population.¹⁵⁴

There seems to be some confusion as to whether Black people of African extraction suffer from the disease. Some sources state that it is rare amongst Africans, and there are few cases in Nigeria.¹⁵⁵ Yet, as was shown earlier, it is not uncommon among Black people in Manchester, UK, or New York, USA. Perhaps more importantly, it is not uncommon

in South Africa, where an incidence of 2.4% in Whites aged 55 years and a prevalence of 1.3% among Blacks in Johannesburg has been recorded.¹⁵⁶ This survey was published in 1988 at a time when there was 1 physician for every 330 Whites but only 1 for every 91,000 Blacks. The life expectancy in 1980 was 55 years for Blacks, 58 years for Coloured's, 65 years for Asians, and 70 years for Whites.¹⁵⁷ Surprisingly, the recorded rate of PDB was high for Blacks, given the prevailing conditions at that time. South African coal is low in arsenic and lead, making this an unlikely source of toxic element exposure. Nearly 90% of African coal is mined in South Africa, sometimes used for cooking and heating.¹⁵⁸ However, there was another prominent source of arsenic, related to the many gold mines in that country.¹⁵⁹ Scattered small communities depended on local streams and boreholes in the vicinity of mines for drinking and irrigation water. The sulphide mineral weathering, which accompanies gold mining and processing, resulted in contamination of the water supplies with arsenic.¹⁶⁰ The statistics for PDB in Africa are largely absent, and because of poor medical facilities, many cases would have been missed. If arsenic were a trigger for the disease, there would be few African cases other than those near gold and copper mines. The complete absence of data since a single study in 1988, other than one more recent case in Nigeria, has led to the assumption that PDB is rare in people of African descent.¹⁶¹

Genetic factors.

The AS3MT gene plays a crucial role in arsenic metabolism in humans, specifically in the methylation of trivalent arsenic. This methylation process converts arsenic into less toxic forms, facilitating its excretion. Genetic variations in AS3MT can influence arsenic metabolism efficiency, potentially impacting an individual's susceptibility to arsenic-related health issues, and the Japanese in particular have few mutations to this gene.¹⁶² This gene, which has not been linked to PDB in any way, is more prevalent in some Asian and Andean populations.¹⁶³ Physical activity benefits arsenic methylation, and those populations in the developing world in a predominantly rural environment have high levels of physical activity.¹⁶⁴ The increasing levels of PDB in New Zealand Asians could be partially related to a change in diet and exercise. A high-fat diet affects the SQSTM1 gene, p62, which has been implicated in PDB.¹⁶⁵ Such a diet may cause undesirable bone regeneration.¹⁶⁶ People with the SQSTM1 gene appear to have more severe cases of PDB than those without this gene.¹⁶⁷ Mild cases of PDB may often go undetected.

Smoking and diseases attributed to arsenic.

If PDB is triggered by arsenic, one would expect to find high levels of disease where arsenic is prevalent in the hotspots, and similarly, low levels where arsenic is absent. Arsenic toxicity has been attributed to cases of lung, bladder, and skin cancer.¹⁶⁸ Lancashire has a lung cancer rate 9% above the national average, and the figure for North West England as a whole is 20%. Bladder cancer in Lancashire is 14% above the national average.¹⁶⁹ In 2011, the North West of England had the highest rate of smokers in the country (21.9%).¹⁷⁰ By 2019, Spain had higher levels of smoking than even North West England at that date.¹⁷¹ That country has high levels of lung cancer, particularly among men.¹⁷² Sweden has the lowest rate of smoking in Europe and the second-lowest rate of lung cancer.

In Las Pampas, Argentina, there are high rates of cancer, possibly attributed to pesticide use.¹⁷³ However, the number of smokers remains high.¹⁷⁴ Quebec has the highest rate of lung cancer in Canada and a high proportion of smokers.¹⁷⁵ New Zealand previously had a high rate of smoking, but has been trying to ban cigarettes, and the rate of adult smokers was reported as 8.4% recently.¹⁷⁶ Despite this, lung cancer rates are high compared to other countries with similar healthcare systems.¹⁷⁷ There seems to be a good correlation between high rates of smoking and PDB, except for New Zealand, where smoke from CCA-treated wood may be the most significant factor. Lung cancer is a major cause of death in India. 28.6% of the population (42.4% men and 14.2% women) use tobacco products. By 2025, cases of lung cancer will be 7 times higher than a decade earlier.¹⁷⁸ Recorded PDB cases have started to increase in India.¹⁷⁹

Discussion

The case studies demonstrate a likely connection between exposure to arsenic and PDB, based on the presence of arsenic in the identified areas. It is therefore possible that arsenic, sometimes in combination with other toxic elements such as cadmium, thallium, lead, selenium, and chromium, which cause genomic instability, may have significantly contributed to the incidences of PDB in most instances.¹⁸⁰ It has been suggested that lead may be a cause of PDB, lead being frequently found in coal particulates (it is often high in UK coal), but not so frequently in well water or wood.¹⁸¹ Anyone suffering from PDB caused by coal would inevitably also have high levels of lead in their body, which might

exacerbate symptoms. Lead is unlikely to be involved in cases of PDB found in Italy, Spain, Argentina, and New Zealand. However, arsenic is present in every single recorded case of high levels of PDB, whereas the other elements are not always present.

The effects of arsenic exposure related to the duration and concentration of exposure are unknown. Health effects of arsenic are often divided into two categories: acute, or single-dose exposure, and chronic and long-term exposure. Remarkably little is known about the toxicity of arsenic concerning humans. Most laboratory animal species appear to be far less sensitive to arsenic toxicity than humans; for instance, chronic oral doses that would cause marked effects in humans cause no effect in monkeys, dogs, or rats.¹⁸² Research has concentrated on compounds that act as human carcinogens, and more recently, factors that influence arsenic methylation. Studies have implicated dosage of exposure, an individual's ethnicity, age, sex, body mass index, lifestyle and dietary history, inherited genetic characteristics, exposure to other diseases, and methylation capacity. Some of the studies provide contrasting results, and none are conclusive.¹⁸³

Both the British and Americans were primarily interested in the short-term effects of arsenic poisoning through the release of Adamsite (DM). Once a "volunteer" who had been exposed to tests in a gas chamber left the Army or the secret chemical weapon establishments, such as Porton and Edgewood Arsenal, no follow-up was undertaken, and any claim for long-term health effects was invariably met with a flat denial of responsibility. Many volunteers for trials were exposed to two or more chemicals during their visits to Porton, as there was a shortage of volunteers. This made determining the cause of any subsequent ill health problematic. The records of human "guinea pigs" were perfunctory and not kept for a protracted period, and the health of those filling chemical weapons was never followed up. On 21 July 1998, Ken Livingstone MP asked a number of Parliamentary Questions (PMs) regarding various chemical agents. One of these agents was Adamsite (DM). The written reply was as follows: "I have been asked to reply about short-term exposure to Adamsite (DM). DERA's Chemical and Biological Defence sector (CBD) has not conducted research involving exposure to Adamsite (DM) for over 30 years. No assessment of possible long-term health effects resulting from short-term exposure to Adamsite has been made." Governments of those countries developing chemical weapons would rather not investigate any long-term effects of these weapons, as this might precipitate many claims. Major Thomas Davies DSO MC RE and Lt. Christopher Rowland Alderson, MC MM RE, who suffered repeated exposure to DM particulates in north Russia whilst undertaking tests on the new weapon both

died prematurely of a heart attack. Coronary heart disease is one of the many adverse effects of exposure to arsenic.

Testing a person for exposure to arsenic is often ineffective, or worse, misleading. Blood and urine tests are only valid if used to detect a recent high level of arsenic exposure. Hair analysis, possibly from beards for men, is more accurate, but can still only show exposure in recent months. Testing toenails can indicate high levels of inorganic arsenic but not the organic form. There is some uncertainty as to how long after exposure toenail testing is valid, with estimates varying from five months to as much as six years.¹⁸⁴

The current WHO recommended limit of arsenic in drinking water is 10 µg/l, established at this level because of the practical difficulty in 1993 (but no longer) in “analytical achievability”. No safe level has been set for airborne particles. The incidence of lung, skin, and bladder cancer is the basis for setting recommended levels.¹⁸⁵ Some European countries now specify a maximum of 5 µg/l in water. The original limit (200 µg/l) proposed in 1958 was based on data from smelter workers working at two smelters in the USA and one in Sweden. Emerging international evidence now suggests that chronic human exposure to arsenic at levels below 10 µg/l in drinking water is harmful to health.¹⁸⁶ Low-dose arsenic studies are now ongoing, with continuing debate as to whether **any** dose of arsenic is safe.¹⁸⁷

There are two oxidation states of arsenic. Arsenic III, or arsenite, is the trivalent form of arsenic, with a charge of +3. It is highly toxic and bioreactive. Arsenic V, or arsenate, is the pentavalent form of arsenic, with a charge of +5. Arsenic V is not as toxic as arsenic III, but it still poses a health risk with long-term exposure.¹⁸⁸ Trivalent arsenic compounds include arsenic trioxide and sodium arsenite, while pentavalent compounds include arsenic pentoxide and arsenates like lead arsenate. Water typically contains the more dangerous inorganic arsenic. Coal contains both trivalent and pentavalent inorganic arsenic. The chemical warfare agent, DM, also known as Adamsite, contains the very toxic trivalent form of arsenic. There are a number of striking similarities between arsenic and its known properties and PDB, which are listed in the following table.

Properties of Arsenic that affect humans	Similarities of Paget's Disease of Bone
Non-cancer manifestations are numerous and highly variable from one country to the next. ¹⁸⁹	Incidence of PDB varies from one country to the next. ¹⁹⁰
Found in tobacco. ¹⁹¹	Bone disease is linked to smoking. ¹⁹²
Calcium and vitamin D are beneficial, minimising toxicity. ¹⁹³ Arsenic diseases are affected by nutrition. ¹⁹⁴	Calcium and vitamin D are beneficial if deficient. ¹⁹⁵ PDB has decreased as nutrition improves, but less so in deprived areas with poor nutrition. ¹⁹⁶
Men have less efficient methylation than women. ¹⁹⁷	PDB is more prevalent in men than women. ¹⁹⁸
Long latency (up to 40+ years) between arsenic exposure and bladder/lung cancers. ¹⁹⁹ Methylation is reduced as from the age of 50. ²⁰⁰	Long latency of up to 40+ years between toxic exposure and onset of disease. The disease is rarely seen before the age of 50.
Rapid decline in arsenical particulates in the UK since 1960 but starting in 1926 with the Public Health (Smoke Abatement) Act. ²⁰¹	Rapid decline in PDB in the UK since the 1970s, some 40-50 years after smoke control was introduced. ²⁰²
Arsenic raises ALP (alkaline phosphatase) activity. ²⁰³	Patients with PDB often have raised ALP levels. ²⁰⁴
Decreases bone mineral density, and arsenic trioxide interferes with bone remodelling. ²⁰⁵ Affects osteoclasts and osteoblasts.	Caused by abnormal activation of osteoclasts. Osteoblasts produce new and defective bone. ²⁰⁶
It can cause osteoarthritis. ²⁰⁷	It can cause osteoarthritis. ²⁰⁸
The role of carbohydrates, low intake of micronutrients, and poor nutritional status increases the risk of arsenic disease. ²⁰⁹ Heavy drinking and use of tobacco lowers methylation. ²¹⁰	Those living in areas of deprivation have a higher incidence of PDB. ²¹¹ Sufferers are advised to avoid heavy drinking and the use of tobacco. ²¹²
Arsenic exposure can disrupt cellular processes involving the SQSTM1 (also known as p62) protein, which is involved in autophagy. ²¹³	Mutations of the SQSTM1 gene are linked to PDB. ²¹⁴
Arsenic inhibits DNA repair and interacts with zinc finger proteins. ²¹⁵	Regulation of the human zinc finger gene ZNF687 associated with PDB. ²¹⁶
Curcumin attenuates the harmful effects of arsenic. ²¹⁷	Actions of curcumin may be therapeutic in bone disorders. ²¹⁸
Arsenic exposure has been linked to lower measles antibody titers, particularly in boys with low serum folate levels, potentially reducing protection against the disease. ²¹⁹	The decreasing incidence of PDB linked to measles vaccination has reduced cases of measles. ²²⁰
People of Aymara-Quechua ancestry appear to have adapted to high arsenic levels. ²²¹	PDB is uncommon in Andean regions. ²²²

Table 2. Comparison of the effects of arsenic ingestion and PDB.

There are many medical conditions associated with arsenic, such as skin problems, certain cancers (lung, bladder, and skin), heart disease, and diabetes. From the available data for the hotspots or general areas covered, most countries or areas with high rates of PDB seem to have recorded high levels of lung and bladder cancer.²²³ Hungary and Serbia have the highest rates of lung cancer in Europe. They also have high levels of arsenic in the water, and the people there are heavy smokers. However, it appears that Balkan people do not have the genes that make them particularly susceptible to PDB. Because lung and bladder cancers are associated with smoking, it is difficult to identify the causes of these cancers unless statistics indicate cancer rates for non-smokers exposed to arsenic in the air or water. The impact of arsenic from other sources has not been properly considered for the 10-20% of lung cancer cases that cannot be attributed to smoking.²²⁴

The incidences of PDB suggest that long-term exposure may be linked to the disease, but the definition of “long-term” remains problematic. At the chemical weapons filling station in Morecambe, exposure was for 6 months for some employees and 10 months for others. Major Davies was to proudly state in a report produced in April 1919 that no employee had suffered health issues, unmatched in any other chemical weapons facility.

There are several reasons to be concerned about future instances of the disease, which have declined in recent years. Firstly, the dumping of arsenic-based chemical weapons in the seas and oceans, and the corrosion of the casings of these weapons. The casings of WW2 air-dropped chemical weapons were quite thin to save weight. Chemical weapons (CW) were produced in mass quantities during both World Wars; however, those made during World War 2 were never used in battle in the European theatre. Nevertheless, vast quantities of chemical warfare agents (CWA) were manufactured, the Soviet Union and USA continuing to do so until 1969. The largest part of those captured by Allied armies, as well as some Russian ones, were dumped in the Baltic Sea and Skagerrak Strait on the orders of the British, Russian, and American occupation authorities. Phenyl arsenic-containing chemicals in the dumped munitions and containers were Clark I and Clark II (WW1 only) and DM/Adamsite, and Lewisite (the Lewisite often mixed with mustard gas).²²⁵ Activities such as bottom trawling, the construction of undersea pipelines and cables, and the building of wind farms are increasingly claiming space within the contaminated areas where the contents of the munitions are starting to leak.²²⁶ British

chemical weapons were dumped in Beaufort's Dyke in the Irish Sea (between Scotland and Northern Ireland) and the Atlantic Ocean, northwest of Ireland. French weapons were dumped in several locations, including just 40 miles off the Dunkirk coast and the coast near Toulon. Japanese chemical weapons were dumped off the coast of Japan. Those from the USA were dumped in both the Atlantic and Pacific Oceans, and most Russian ones were dumped in the White Sea and various other Arctic seas and Siberian lakes. Complete natural degradation of arsenic chemicals is estimated to take as long as 100 years once released.²²⁷ Crustaceans and bottom-dwelling fish are likely to absorb arsenic if in the sediment on the seabed, and these should be frequently tested for arsenic if harvested.

Some countries, such as Vietnam, Cambodia, Myanmar, Bangladesh, and the West Bengal area of India, have high levels of arsenic in the groundwater. The WHO has declared exposure to arsenic in groundwater “a major public health concern”.²²⁸ In rural areas, much of the population in these areas rely on tube wells installed since the 1970s to reduce disease from ingestion of pathogen-laden surface waters. In Vietnam particularly, these wells, which were installed in the 1990s, were necessary to avoid the contamination of surface water by the chemicals used as herbicides in the war. Korea previously had a very low rate of Paget’s Disease, but this is now increasing, especially amongst women.²²⁹ The effect of arsenic poisoning has already caused many cases of debilitating and fatal illness, and may, in the future, cause PDB for those who survive these other diseases if genetically susceptible. Some health experts have called arsenic poisoning through water contamination “the biggest mass poisoning in history”.²³⁰

Climate change is causing sea levels to rise, with saline water polluting low-lying areas. There will be more devastating floods and more frequent severe droughts. Pumped water from tube wells with high levels of arsenic will be used to provide irrigation during droughts and incursions of saline water. Rice is particularly susceptible to arsenic, absorbing it through its root system.²³¹ High levels of cancer are predicted by 2050.²³² Every day, more than 140 million people in southern Asia drink groundwater contaminated with arsenic. Rice is exported to countries where rice is not grown, and checks for rice products, which include rice cakes and rice milk, may not always be thorough. Rice milk arsenic levels exceed EU statutory water limits.²³³ This could be an issue for those who regularly consume rice or rice-based products, those with some Asian ancestry who now live in the West being noteworthy.

Climate change may increase the levels of arsenic in groundwater, affecting it by altering recharge, flow dynamics, and water quality. Any deterioration of groundwater quality may threaten the sustainability of drinking water supplies, particularly in groundwater systems prone to geogenic contamination such as fractured bedrock aquifers. This will primarily affect those people dependent on well water.²³⁴ Increasing temperature and flooding enhance arsenic release and biotransformations in arsenic-rich soils, which are very sensitive to an increase in temperature.²³⁵

Fly ash from coal was, until the introduction of electrostatic precipitators in the mid to late 20th century, heavily contaminated with heavy metal elements, particularly arsenic. This ash has been dumped in large waste tips beside many abandoned coal-fired power stations.²³⁶ Colliery spoil, the waste material from coal mining, can contain arsenic, along with other heavy metals, posing a risk to the environment and human health. Most of these tips and lagoons are unlined, and toxic elements can leach into the water table.²³⁷

Climate change will also increase the incidence of wildfires – this is already self-evident. Wildfires can release arsenic into the environment from contaminated soils (particularly waste from mines) and vegetation. The airborne particulates can spread for hundreds of kilometres.²³⁸

Because of climate change and air pollution, there is a trend to transition from ICE to EVs (electric vehicles), which use three to four times more copper than conventional vehicles. Solar energy and wind power both use large amounts in their construction and provision of the necessary electricity grids. The rapidly developing data centres and AI also use large amounts of copper, using perhaps 7% of production by 2050.²³⁹ Whilst this metal can be recycled, there will still be a need for many new copper mines. The global shortage of copper presents a significant challenge to the energy transition and the broader sustainable development goals. A study has highlighted the need for the establishment of between 35 and 194 large new mines over the next three decades. Many of the best grade ores have already been exploited, requiring more low-grade “contaminated” ores to be mined.²⁴⁰ Arsenic cannot readily be extracted from mineral ores, and a process known as blending is used, mixing the contaminated ores with cleaner ones during smelting. This

will soon no longer be sustainable as the quality of the ore decreases and the emissions from copper smelting plants are an increasing cause for concern.²⁴¹

The potential health effects of exposure to airborne arsenic-bearing particulates generated by current and/or past mining operations are widely recognized as a growing issue of significant global importance.²⁴² Waste arsenic is typically dumped in tailings. In many abandoned gold and copper mines, these tailings were left at the surface or just below, sometimes held back with a tailings dam, where they remain.²⁴³ At the copper smelting plants, much of the waste arsenic ends up in slag. Globally, about 30-37.7 million tons of copper slag are produced annually, much of it simply left in dumps or pits.²⁴⁴ Intense rainfall, now increasingly violent and frequent, could cause tailings sediments and slag to escape into streams and floodplains, polluting wells, farmland, and gardens.

Acid mine drainage (AMD) occurs when polluted water from mines (many abandoned) flows over pyrite. The very acidic water contains heavy metals, particularly arsenic. It leaches into aquifers, flows into streams, and spreads over flood plains, sterilising soils and contaminating food crops. AMD has recently been named the second most important global concern after global warming by the United Nations.²⁴⁵ It is a global environmental crisis, and because of the vast number of abandoned mines and collieries with no current owner, some dating from Roman times, tackling it is problematic, particularly in places such as the UK, Spain, and South Africa.²⁴⁶

CCA-treated timber in New Zealand and elsewhere should be disposed of in licensed landfill sites that are sealed to prevent contamination of groundwater. In most countries that have used treated timber, there are insufficient sites to cope with the vast quantities of contaminated timber that will need to be disposed of in the future.²⁴⁷ The location of such tips may not be widely known, and they may be too distant for many people to use. This is likely to lead to the contamination of groundwater with arsenic.

Prevention is, of course, better than a cure. Whilst there is no cure for the disease, its onset may be slowed or even prevented, and this is a field for future research. Arsenic diseases are linked to poor nutrition, and as this has improved since the 1950s, so has the rate of PDB diminished.²⁴⁸ There may be practical measures that those deemed at risk can

take. Keeping fit and taking regular exercise may be important.²⁴⁹ Folic acid, vitamin B12, choline, betaine, and creatine all assist with the methylation of arsenic.²⁵⁰ Selenium may also assist, depending on the dosage.²⁵¹ Curcumin can beneficially affect the skeletal system. Plant-based formulations can not only offer protection against arsenic-mediated toxicity but can also serve as a therapeutic formulation to reverse the toxic effects induced by arsenic.²⁵² The effectiveness of these supplements may vary depending on individual factors, such as a person's genes, age, arsenic exposure levels, and pre-existing nutritional status.

Conclusions

The book *The Molecular Biology of Paget's Disease*, edited by Paul T Sharp and issued in 1999, states in the introduction that PDB receives scant attention from the medical community and public alike, calling it a "Cinderella" of diseases.²⁵³ Notably, much of the available survey data was collected 30 to 50 years ago, with little more recent data. The early stages of disease are often unrecognised, and, in many countries, the medical profession may be unaware that there is such a condition and may fail to undertake appropriate tests. It is mainly thanks to the ongoing work by The Paget's Association in the UK that it is more widely known in certain English-speaking countries. Most recent research has concentrated on genetic susceptibility and not environmental causes.²⁵⁴ The case for genetic susceptibility is proven, and research continues to identify implicated genes, but there also appears to be an environmental trigger in the majority of cases. Theories as to what the environmental factor or factors might be have so far been speculative and inconclusive.

This paper shows a link between PDB and levels of arsenic either in the air or in the water in a particular locality, reviewing many of the hotspots and ancient cases which have been recorded in earlier research. The disease has declined in line with reduced emissions of arsenic in the air and the decrease in cigarette smoking. However, in locations where arsenic is present in well water, and where these wells continue to be used (Italy, Spain, and Argentina), there has not been a corresponding decrease. The disease has reduced in New Zealand and Quebec Province, but records only show this has happened over the last two decades or so.²⁵⁵ There are striking similarities between the effects of arsenic and PDB. Unfortunately, if this link between PDB and arsenic is proved, the current levels of

PDB may be a temporary respite. Some of the statements or hypotheses about the disease need to be challenged or investigated further regarding theories on the cause of the disease, as well as its predominantly limited occurrence among those of Anglo-Saxon descent.

Men are more likely to suffer from PDB than women, as in the past, more men worked in heavy industry, and a high percentage drank alcohol and smoked. All these factors impact one's ability to methylate arsenic.²⁵⁶ Women generally have higher levels of DNA methylation compared to men, which may be significant. The difference in rates of PDB between men and women has diminished as equality between the sexes has increased. People in deprived areas are disproportionately exposed to concentrations of pollutants higher than in less deprived areas, particularly in UK regions such as the Northwest, Yorkshire, Humberside, parts of Cornwall, and London. Rates of PDB are higher in such areas.

Arsenic can become even more toxic when combined with microplastics and heavy metals, such as lead, chromium, selenium and cadmium, as the combined exposure can create a synergistic effect, meaning the overall toxicity is greater than the sum of each substance's toxicity alone; this is because they can interact at the cellular level and amplify harmful effects on the body.²⁵⁷ This is another area where further research is required. It is possible that cadmium, on its own, could also cause PDB.

Acceptable levels of arsenic in the environment provided by the World Health Organisation (WHO) and national authorities have been primarily based on the need to avoid excessive cases of skin, lung, and bladder cancer. Arsenic has been attributed to a significant number of health issues, and much further research is needed, as outlined in a paper published in 2015.²⁵⁸ Most research on the adverse impact of arsenic since that date has concentrated on the incidence of arsenic in groundwater in Southeast Asia. As more information has become known, the "guideline" levels for acceptable concentrations in water have been progressively reduced and may yet need to be reduced further.²⁵⁹ The WHO and national agencies have been reluctant to set lower targets for arsenic without proof that these are necessary, there being considerable cost and practical issues should they do so. Similar issues were encountered with other toxic materials, with the need to have indisputable proof before acting to remove lead from fuel, mercury from the

environment, to ban the use of certain pesticides and herbicides, to restrict the use of plastic bags (microplastics), and to ban and remove asbestos. Dissuading people from smoking cigarettes is, of course, ongoing, but few now dispute the link with certain cancers.

The current regimes that test for arsenic in the air, in water, and in food are frequently inadequate, with the so-called acceptable, or even “safe”, levels based on limited information from possibly suspect data presented more than twenty years ago.²⁶⁰ More research is required to find the levels and duration of exposure to arsenic and the relative toxicity of contaminated air and water, which can cause disease.²⁶¹ Many environmental agencies are under-resourced and under-funded, with testing for arsenic not being high on their agenda. The air monitoring that they undertake usually just measures hydrogen sulphide (H₂S), methane (CH₄), oxides of nitrogen (NO_x), sulphur dioxide (SO₂), and sometimes different particulate matter sizes, but not toxic elements. Wood fires, using so-called “green” fuel, now cause more air pollution in winter than vehicle exhaust in many urban locations, the smoke frequently containing fine particulates with arsenic.²⁶² The danger of sawing, burning, or spreading ash from CCA-treated wood needs to be given more prominence, particularly in Greece and New Zealand. Also important is the disposal of treated timber in suitable lined tips, to prevent contamination of groundwater.²⁶³

Unless the dangers of using untested and untreated well or borehole water, and burning CCA-treated wood, are taken more seriously, the incidence of PDB, if it is indeed linked to arsenic exposure, may not decrease much further in certain locations with high rates. Individuals living near abandoned heavy metal mines, smelting plants, cement plants, waste incinerators, pulp and paper mill plants, and chemical works that use arsenic-based ingredients may be at risk. Those repeatedly exposed to smoke from forest fires, such as fire-fighters and residents in fire-prone areas, may also be at risk and must be encouraged to wear appropriate masks in smoky conditions. Industries using arsenic-based compounds include those involved in the production of electronic components, special alloys, and the manufacture of certain glass and ceramic products. Those people genetically susceptible to PDB should possibly avoid working in or living near such facilities. Some disintegrating chemical weapons contain arsenic, and seafood from the areas where these have been dumped may be contaminated. Regular checks of arsenic levels in seafood in these areas should be mandatory.

Arsenic sulphides and other rocks contaminate the ores extracted when mining for silver, gold, lead, zinc, rare earths, and in particular, copper. To meet projected global copper demand by 2050, including that needed for the energy transition, some studies suggest the need for 194 new large copper mines or an average of 6 new mines annually.²⁶⁴ Smelting operations for the above elements often produce considerable quantities of arsenic. Smelting plants are now the largest emitter of airborne particulates containing arsenic.²⁶⁵ New technologies must be used to limit the emission of arsenic from these smelters.²⁶⁶

Abandoned mines with their tailings and piles of toxic waste will become an issue with increasing frequency owing to flash floods caused by climate change. Unauthorised gold mines in Africa and Amazonia in South America are leaving behind a trail of toxic material containing arsenic, which will, in the future, cause health issues, possibly including PDB, in these areas.²⁶⁷ This seems to be an intractable problem.

As DNA testing becomes more widely practised, those people considered genetically susceptible to PDB might be advised to take supplements to assist with arsenic methylation, as from the age of 50, an age at which methylation starts to decline. Further research is required to see if such an approach is worthwhile. As with many diseases, regular exercise, a healthy diet, and drinking and particularly smoking in moderation appear to be good strategies to adopt to reduce the risk. If one has a familial connection to PDB and is concerned that any future offspring may contract the disease, there is always the choice to partner with someone who has Asian or South American Indian genes, as these people are less susceptible to the disease.

There is a systematic lack of knowledge about those PDB studies that are not written in English.²⁶⁸ Hopefully, the translation tools now available for electronic articles will assist in future research. Ongoing research into PDB is essential, coupled with a need to ensure that the medical community is better informed about this disease, which may be more common than very limited and outdated statistics suggest, particularly in developing countries. Those experiencing exposure to high levels of arsenic may suffer from lung, bladder, or skin cancer, succumbing to these before PDB is diagnosed. If and when future cancer treatments prolong life, particularly in developing countries, PDB may start to

become more apparent. PDB may become more prevalent in areas previously thought to be largely immune, such as in South Asia, now experiencing high levels of pollution and arsenic in water supplies. South Africa is a particular country of concern, and more studies are required there for rural areas populated with gold mines. PDB could, in future, come out of the shadows as a “Cinderella” disease, but because of the latent delay in symptoms, a failure to act now to mitigate the causes, taking appropriate measures, could result in more widespread and numerous cases of the disease in countries with populations having poor nutrition and suffering from poverty.

With Caucasians from Western countries increasingly visiting or relocating to Asia, often having a relationship producing inter-racial offspring, this may now produce more cases there. On the other hand, children with mixed Caucasian and Asian or South American blood may be less susceptible to the effects of arsenic, or at least, the severity of PDB. In a similar manner, many people of Asian extraction have relocated to Australia and New Zealand. Both these countries have a high rate of PDB and a high rate of lung cancer. Recent studies have shown that the high rate of lung cancer can no longer be attributed to smoking and that some other environmental factor must be responsible. Asians appear to be more susceptible to suffering from lung cancer than those of other races, and in New Zealand, Asians also appear to have a higher rate of PDB than would be expected. Both Australia and New Zealand have made extensive use of CCA-treated timber, and surprisingly, New Zealand continues to do so despite reservations and a ban in most other countries. The Asian diet contains a large amount of rice, and although some of this rice is grown in Australia, the recent lack of rainfall has resulted in most of this being imported from Vietnam and Thailand, and to a lesser extent, India. Vietnam suffers from high levels of arsenic in groundwater and from Agent Blue used by the USA in the 1960s. Northern Thailand has water polluted with arsenic, a result of mining, particularly tin mining. Grown in flooded conditions, rice absorbs arsenic from the soil and irrigation water, a practice unique to rice crops among most food crops. Rice accumulates inorganic arsenic, which is the toxic form. The consumption of even low amounts of inorganic arsenic through food or drinking water can lead to cancers and a range of other health problems, such as cardiovascular disease, diabetes, and possibly PDB.

From 1950 to 1970, calorie malnutrition and specific vitamin deficiencies fell sharply in high-income countries because of economic development and large increases in low-cost processing of staple foods fortified with minerals and vitamins. Food affordability has also changed, with few people going hungry in developed countries. Levels of pollution have decreased considerably in the developed world but are now increasing in some developing countries. It does appear that the incidence and severity of PDB in those countries recording such data have diminished since the mid-1970s, particularly since 1999.²⁶⁹ Nutritional status has not changed much in the last 25 years, so perhaps we can expect the decline in PDB now being recorded in high-income countries to cease quite soon and the rate to plateau, with a majority of non-genetic, environmentally caused cases occurring in low-income areas. Should climate change, wars, volcanic eruptions, unsustainable farming practices, pests, or diseases cause crop failures, future poor nutrition could result in an increase in the instances of PDB in those countries impacted. As physicist Nils Bohr is said to have remarked, “Prediction is very difficult, especially if it's about the future”.

Data indicates that Paget's disease of bone has been with us since ancient times and was even present in a dinosaur from the Late Jurassic period (150 million years ago).²⁷⁰ Why should such a disease disappear, almost overnight, in evolutionary terms? To truly establish beyond doubt the environmental cause of the disease, a multidisciplinary approach may be required with epidemiological studies having input not only from various medical disciplines but also from statisticians, geneticists, social historians, atmospheric chemists and chemical engineers, hydrologists, hydrogeologists, agricultural scientists, palaeontologists, and mineralogists. Because of the way science and medicine are traditionally organised, that is some challenge.

Many research papers provide interesting theories, but all too often, these are never followed up. The obvious question is “what next?”. Does this paper reside along with others that have left the cause of PDB unresolved, but with interesting theories? It would be helpful if arsenic could either be ruled out or identified as a likely cause. If the latter,

those at risk or in the early stages of disease could take measures to assist the methylation of arsenic, either preventing or slowing the disease. DNA analysis can now detect damage or mutations that may indicate the likely cause as arsenic.²⁷¹

There is a Canadian town that has had, until recently, high levels of atmospheric arsenic, and that is Rouyn-Noranda in Quebec Province, home of the Horne smelter.²⁷² Air pollution from a copper smelter in Tacoma, Washington State, USA. previously contained arsenic, which settled on the surface soil of more than 1,000 square miles of the Puget Sound basin.²⁷³ Arsenic, lead, and other heavy metals are still in the soil as a result of this pollution. PDB statistics for those of European descent living in those locations would help endorse or refute this hypothesis. Cornwall has a rate of skin, lung, and bladder cancer that is well above the average for the UK. Ascertaining the rate of PDB should be a priority for those areas with former mines (University Hospitals Plymouth/Royal Cornwall Hospitals). Establishing the current rate of PDB in New Zealand among those of European descent would also indicate if CCA-treated wood was responsible for any raised incidence of PDB above the UK rate, given that the cigarette smoking rate there is now less than 7% among European men and women, lower than in the UK.

There is rarely such a thing as “certainty” when identifying the cause of a disease caused by a toxic material, particularly when the effects can take up to 50 years or more to surface. A satisfactory probability needs to be established. Epidemiological studies, such as the one undertaken here, must demonstrate a clear association between arsenic exposure and increased risk of PDB. A life history of those suffering from the disease might identify if those persons have lived for more than a few months at any time downwind of coal-fired power stations, glass factories, cement works, heavy metal mines, or smelters and metal processing plants. Other sources of arsenic could emanate from wells, and food grown on land likely to have been impacted by arsenic. A dose-response relationship, meaning that higher levels of arsenic exposure are linked to a greater risk of PDB, would be helpful, but not essential. It is starting to be realised that exposure to levels of arsenic at, or even below, current guidelines may be a contributing factor to many debilitating diseases. It is also known that arsenic can damage DNA, disrupt DNA repair mechanisms, and alter epigenetic regulation of gene expression. The global health effects

of exposure to arsenic are understated and underestimated, with lifestyle and genetic variations being of particular importance.²⁷⁴

For those genetically susceptible to PDB or at the early stage of the disease, nutrition education is important, focusing on an adequate dietary intake of methionine, choline, zinc, folic acid, and B vitamins (B2, B6, and B12). These nutrients, which potentially have modulating effects in iAs metabolism and toxicity, should be used in prevention efforts for populations exposed to iAs.²⁷⁵

Footnotes

Conflicts of interest/Competing interests: The author declares that he has no conflicts of interest or competing interests.

Consent to circulate or use the contents of this thesis: The contents of this thesis may be freely used and disseminated, provided due recognition is given as to the contribution made by the author. This article has been reviewed by Emeritus Professor Timothy Cundy, formerly Professor of Medicine at the University of Auckland. Amendments have been made to the first draft based on his observations (inserted at the end of this paper). It should be made clear that he neither endorses nor disputes my hypothesis.

Revisions.

R1 05/07/2025. Endnote 48 added regarding the population of Morecambe in 1971.

Paragraph inserted on p. 44 regarding the unknown long-term effects of chemical weapons.

Punctuation, grammar, and readability were reviewed and adjusted. Notes on lung, bladder and skin cancer rates added. Recommendation paragraph added at the end of Conclusions.

R2 28/07/25. Minor change to Conclusions.

R3 23/08/25. Mention of cancer in Australia and New Zealand, and possible link to arsenic in the conclusion.

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Comments and observations from Professor Tim Cundy, formerly of Auckland University, New Zealand, regarding first draft of a thesis dated June 2025 by Brian Davies with the title “Paget’s Disease – Is Arsenic the cause?”.

Comment. The most recent PDB prevalence survey in NZ was published in 2009 (attached) and this shows declining rates compared to 20 years earlier – and rates that are comparable to the UK. I believe they would have declined even further now.

Answer. I would like a UK researcher to demonstrate that UK rates in or about 2009 were similar to those in NZ. I believe that those in NZ were higher at that date and remain higher today. Even if this is not the case, the PDB rate in NZ is relatively high.

Comment. Your data on air pollution in the UK and elsewhere is interesting, but the top 8 cities for air pollution are all in the sub-continent where PDB is relatively rare. Not sure where your data that ‘PDB is starting to increase in India’ comes from. There may be more reports, but that’s not a true indicator of prevalence.

Answer. I have explained in the text why data in India and Asia in general show few cases of PDB. Genetics, life expectancy, relatively recent industrialisation, lack of expertise in making a diagnosis, absence of radiographs in many areas. It is true that the increase in cases may be the result of more reports and better-informed medical authorities and further studies are needed.

Comment. You comment on mediaeval ‘hot spots’ p8, but these interred skeletons are, as far as we know, typical of the period of their burial, so they are not really hot spots.

Answer. I am not aware that the medieval cases quoted are “typical of the period of their burial” and seek an opinion by a recognised authority on the subject.

Comment. With regard to the Lancaster anomaly (M vs F) p19-20, the industrial history is fascinating but one does have to be careful over-interpreting small difference which may just be the play of chance.

Answer. If I have “over interpreted” the results, then I am not alone, as the average rate for Lancaster has been quoted by several researchers writing in subsequent papers. This is not a small difference; it is a major difference. Statistics from other towns and cities have been used, and my thesis does not rely solely on the figures quoted for Lancaster.

Comment. Regarding Agent Blue (p33) would one not expect that the Vietnamese people it was dropped on would have more PDB than those doing the dropping?

Answer. Agent Blue was sprayed in three specific rural locations in South Vietnam. Many of the Viet Cong and villagers hiding there would have been killed at some

time or suffer cancer or some other life-shortening terminal disease, before PDB became apparent. The UN estimates life expectancy at birth at 55.8 for the period 1975-79, and at 62.6 for the period 1985-89. The Vietnamese have very high rates of lung and bladder cancer, although it is not possible to attribute the cause specifically to smoking or arsenic herbicide (probably a mixture of both). Southeast Asians, in general, are not genetically susceptible to PDB.

Comment. The AS3MT gene was not identified on large scale genome-wide association studies of PDB genetics (O.Albagha et al Nature Genetics 2010;42:520–524 and 2011;43:685–689).

Answer. That is precisely the point I make! Those with this gene or certain mutations of this gene appear to have resistance to the disease. The fact that this gene has not been associated with PDB in any way supports my thesis. The AS3MT gene is involved in arsenic metabolism,

Comment. It's quite possible that arsenic may have different effects according to the route of absorption (gastrointestinal, inhalation, skin) so this is a confounding factor. And as you point out, there are areas where arsenic levels are high but PDB prevalence is low. Is there a plausible or testable scientific explanation for this, or does it mean the arsenic hypothesis is incorrect?

Answer. There is no doubt that people with certain genes, primarily but not exclusively originating from Western Europe, are more susceptible to PDB. I am not aware of any instances where Caucasian people exposed to high levels of arsenic lived in areas with a low prevalence of PDB. If there is undiscovered PDB data from those places with gold, tin, or copper mines that have contaminated ores containing arsenic (other than in the Andes), this would be significant. It has been established that Andean people have a high resistance to arsenic toxicity. If residents living downwind of smelting plants (e.g., Walsall, UK, and Washington State, USA) were tested for PDB, that would be helpful.

There are many unknown effects of arsenic as outlined in the WHO factsheet on arsenic. This factsheet states, "The symptoms and signs caused by long-term elevated exposure to inorganic arsenic differ between individuals, population groups and geographical areas. Thus, there is no universal definition of the disease caused by arsenic. This complicates the assessment of the burden on health of arsenic. Similarly, there is no method to distinguish cases of cancer caused by arsenic from cancers induced by other factors. As a result, there is no reliable estimate of the magnitude of the problem worldwide".

Just because there are many unknown effects, that is not a good reason to dismiss this hypothesis that arsenic could be a trigger for the disease. In the absence of a testable scientific explanation based on experiments with animals, statistical analysis and probability may have to serve. PDB is not unique in this respect; there are several medical conditions thought to be caused by arsenic and other toxic elements, such as cadmium, without a testable scientific explanation (various cancers, heart disease, peripheral neuropathy, and diabetes). Arsenic is known to generate multiple types of DNA damage, including oxidative DNA damage and strand breaks. At lower concentrations, studies show that arsenic functions as a co-carcinogen, enhancing the genotoxicity of other DNA-damaging agents. With the advent of inexpensive and fast DNA testing, this may be a way to prove a link if PDB can be associated with damaged DNA.