The hidden history of hypersensitivity pneumonitis

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Examining historical accounts of hypersensitivity pneumonitis and its causes not only considers when first cases were recognised, but also why it emerged at specific times and places, providing insights relevant to mechanisms and disease prevention https://bit.ly/3fKhvCy

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Abstract

Hypersensitivity pneumonitis (HP) is a relatively new construct, first reported in the early 20th century, despite major aetiological factors (farming, bird husbandry) having been part of human activities for millennia. Initial confirmed HP reports included exposure to farming and forestry (1932) and bird exposure (1965), much more recently than is often assumed. Later changes in occupational and living practices have led to HP associated with isocyanates, machine coolants, indoor mould, hot tubs and other exposures. Evolution of our pathological understanding of interstitial lung disease in general, wider computed tomography utilisation and advances in immunology and genomics have shaped our modern conceptualisation of HP. Examining historical accounts of HP and its causative factors not only considers when the first cases were recognised, but also explores why the disease emerged at specific times and places, and may provide further insights relevant to the mechanisms underlying HP and disease prevention.

Introduction

Occupational and environmental hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) associated with aberrant immunological responses to a range of antigens. Research into HP involves understanding which antigens are causative and why exposure to certain antigens (and not others) results in the typical hypersensitivity reaction. Such knowledge aids in arriving at an accurate diagnosis and guides remediation and prevention of progression of disease. However, these tasks often go unaccomplished, with failure to identify a causative exposure in 20–60% of cases [1, 2]. Better delineation of why this immunological reaction occurs may help us develop treatments targeting HP.

Exploring the historical context of HP aids understanding of not only which antigens are causative, but also how important alterations in risk factors that have occurred over time have influenced its development. Remarkably, the history of this disease is largely obscure. Accounts or attributions of the “first reported” cases of HP are frequently cited in reports and reviews of HP, in some cases incorrectly claiming that the history of the disease can be traced back to the 18th century or even earlier. The nature of this literature, much of it pre-dating reliable capture by online databases such as PubMed or Embase, requires the use of “snowball” and hand searching, including that of historical texts [3]. Careful interrogation of the actual sources repeatedly cited in later reports and reviews, and identification of sources uncommonly cited, indicates that this disease is actually a relatively modern construct, dating only to earlier decades of the 20th century. This may be surprising, given that major aetiological factors implicated in HP are characterised by multiple, predominantly agricultural occupational tasks that have been a part of human activities for millennia. However, as we highlight in this review, it is difficult (if not impossible) to discern in historical accounts between what might be HP as distinct from other pulmonary disease processes, in particular work-related asthma, bronchitis or mycotic infections.

Examining historical accounts of HP and its causative factors not only considers when the first cases occurred, but also poses the deeper question "Why did HP emerge in that time and place?" In this review, we ask whether HP is truly an "old" disease, present even from antiquity, or, rather, a relatively modern pathology? If the former case, perhaps it has been present for centuries, but simply called by other names? If the latter, was the emergence of HP due to changing practices or technologies that either generated higher delivered exposures or provided diagnostic modalities, including radiographic imaging and immunological testing, that allowed disease recognition and changed its conceptualisation? Exploring the answers to these questions, consistent with the goals of a scoping review rather than a traditional systematic review [4], may provide further clues relevant to the mechanisms underlying HP and, paramount to health protection, primary disease prevention.

Ramazzini's worms

Respiratory disease in agricultural workers has been described since at least the early 16th century. Olaus Magnus (1490–1557), a Swedish writer and Archbishop of Uppsala, best known for his work 'A Description of the Northern Peoples, 1555', warned:

> …take care when separating the chaff from the grain to prevent it from hurting the vital organs of the threshers, for this dust is so fine that it enters the mouth almost unnoticeably and builds up inside a person's throat to such an extent that, if there is no opportunity of swallowing a drink of fresh beer to give quick relief, he will never eat anything again, certainly no more than a morsel of the corn he has threshed… [5]

Bernardino Ramazzini (1633–1714), in his seminal treatise 'De Morbis Artificium Diatriba' (Diseases of Workers), also commented on grain workers:

> The men who sift and measure [grain] are so plagued by this kind of dust that when the work is finished they heap a thousand curses on their calling. The throat, lungs and eyes are keenly aware of serious damage; the throat is choked and dried up with dust, the pulmonary passages become coated with crust formed by dust, and results in a dry and obstinate cough…and almost all who make a living by sifting or measuring grain are short of breath and cachectic and rarely reach an old age… with inflamed watery eyes, and the dust moreover is so irritating that it can cause a rash similar to nettle rash (hives)…and that these "imperceptible worms" cause "great heat and itching to the body". [6]

Although these accounts point to the respiratory-related risks of farming, the clinical descriptions are far more consistent with an asthmatic or bronchitic illness, rather than HP. The accompanying pathological descriptions provided are the "imperceptible breed of little worms" of what Antony van Leeuwenhoek appropriately called "little wolves" found in the grain and the microscopic appearance of "small white maggots, provided with two red pincers, organs like teeth…" [7], probably consistent with dust mites.

Despite the long recognition of agricultural-related lung diseases, the first clear clinical report of HP was not until the 20th century. In 1932, an astute and original observation was made by UK physician, Munro Campbell, following a "particularly damp hay making season in Westmorland" [8]. Although brief, his report clearly describes at least five cases in farm labourers who developed dyspnoea, mild fever and dry rales on examination. Radiographic imaging showed "fine granular stippling reminiscent of but much finer than silicosis, with some fibrosis spreading to the hilum…some months later, X-ray films now showed very little stippling, but an increased tendency to fibrosis" [8, 9] (figure 1). These cases were found to be negative for other diseases such as tuberculosis, and, in at least one case, fungus was found in sputa, as well as *Aspergillus* spores found in the hay dust [8].

Initially this condition was simply termed "acute symptoms following work with hay" [8] by Campbell. He worked with radiologist Richard Fawcitt who, in a subsequent publication, provided further details on Campbell's series and own accounts of the disease, and termed it "broncho-mycosis feniseciorum (of haymakers or harvesters)" [9]. Fawcitt also noted the similarities and differences of this disease associated with "organic dusts" with that of "inorganic dusts" such as silicosis and other pneumoconiosis. Ultimately, it was another country doctor, W.N. Pickles, in describing his series of several farmers who upon working with mouldy hay developed similar symptoms and chest radiography appearances, and which abated upon

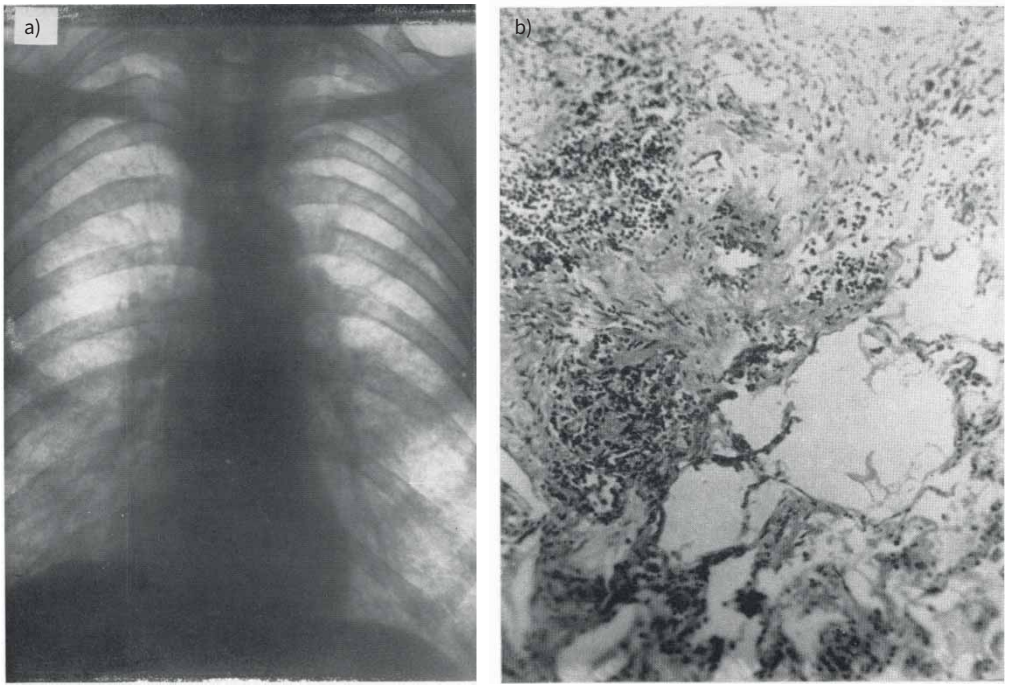

FIGURE 1 a) Chest radiograph showing "fine mottling and fibrosis throughout the lungs"; b) the corresponding case's lung autopsy slide showing "emphysema, patches of lymphocytic infiltration and very marked, patchy fibrosis" from the first reported HP series by Campbell [8], 1932. Reproduced from [8] with permission.

avoidance, "thought it should be called farmer's lung" [10]. Farmer's lung (thresher's lung in some of the European literature) has remained the dominant term since.

Remarkably, nearly simultaneously to Campbell's initial report in December 1932, another report of a new ILD linked to organic matter, emerging on the other side of the Atlantic, was published earlier the same year by the *Journal of the American Medical Association* [11]. In that article, Towey *et al.* [11] described 10 workers who were exposed to *Coniosporium corticale* (now called *Cryptostroma corticale*) while preparing railway ties (sleepers) from maple bark. As the authors described, "owing to the economic depression, the maple trees were [felled] 1 to 2 years ago, and carried through a hot and moist summer which would be favourable to the growth of fungus". 35 out of 200 maple bark strippers developed dyspnoea, wheeze, rales and cyanosis that season, which improved on avoidance and re-presented on re-exposure. Chest radiographs demonstrated a mottled appearance similar to pneumoconiosis with a basal predominance [11]. The authors paired this case series with experiments in which guinea pigs were inoculated with the spores, and on histological examination noted the formation of giant cells and infiltrates of fibroblasts, concluding that this was a new type of hypersensitivity reaction. Maple bark stripper's disease was understood by Towey *et al.* [11] as a unique process and was not recognised as HP until three decades later. From a historical perspective, maple bark stripper's disease can be considered closely linked to the initial recognition of farmer's lung, both first identified in the early 1930s as an agricultural worker's HP associated with contamination by micro-organisms.

Beyond hay-making and bark-stripping, HP associated with other agricultural exposures were additionally recognised from the mid-1930s through the end of the 1960s. The earliest of these was paprika splitter's lung, first noted in 1935 [12]. The initial published report of bagassosis due to contaminated sugar cane debris first appeared in the early 1940s [13]. However, a later historical review of that topic noted that the initial outbreak was linked to the use of bagasse (residual fibrous pulp following sugarcane juice extraction) in a new manufacturing process for an insulating board (called Celotex) that began in New Orleans in 1922. Prior to that, bagasse had either been burned for fuel or discarded. Commenting on the delay between the 1922 and clinical disease recognition, the report notes that this "was not attributable to the sudden appearance of disease *de novo*, but rather to a failure to recognise and later to publicise instances of the disorder that had occurred in earlier years" [14]. The second outbreak of the disease was

reported in Great Britain in 1942, linked to bagasse imported from Louisiana for similar board manufacturing. In that episode, disease was linked to another technical change:

> When manufacture was first started in England the bale-breaking was carried out under water. The process was slow, however, and about 2 years ago machinery was devised for breaking the bales in a dry state that proved to be much more rapid but gave rise to a great deal of dust, some very finely divided, in the air near the machinery. [15]

Other early agricultural-associated HP outbreaks, first reported in the following two decades, include suberosis (cork) [16], mushroom worker's lung [17], disease in malt workers [18], sequoiosis [19] and disease in mould-exposed cheese workers [20].

Meanwhile, by the 1950s several additional detailed case series of farmer's lung were published, documenting the characteristic exposure and clinical and radiographic findings still considered diagnostic today [21]. These early series paved the way for Jack Pepys' work in the 1960s, in which he isolated farmer's lung hay antigens and developed a serum precipitins test using similar techniques (Ouchterlony and double-diffusion tests) that are still used [22]. As a further advancement, in 1963, Williams [23] used these antigens in a provocation test in affected patients to produce similar pulmonary and systemic manifestations akin to farmer's lung.

Although farmer's lung remains an important and arguably one of the most widely appreciated classes of HP, its reported incidence has decreased over time. This decline is thought to be due, in part, to changes in farming practices. "Wringing freshly cut hay of its moisture before storing, equipping hay barns with huge fans that act as dryers, and wrapping hay bales in plastic to prevent the entry of oxygen required for *Saccharopolyspora rectivirgula* growth" [24], are all successful measures to improve yields and, as a side benefit, also reduces the development of microbial overgrowth in hay that promotes HP [24] (figure 2). Changes in practice in sugar cane byproduct handling (*e.g.* spent cane burnt for fuel rather than repurposed) and the general decline in natural cork use may account for declining HP due to those causes.

Birds, fungi and beyond

As a contrast to farmer's lung, recognised since the 1930s, the first unequivocal report of bird-related HP did not appear until 1965 [25]. In that year, Reed *et al*. [25] reported three cases of young male pigeon breeders who developed a febrile illness and a fine diffuse interstitial pneumonia on chest radiographs, all of which cleared after avoidance of exposure and returned upon provocational re-challenge.

This late recognition is all the more remarkable given the long-standing history of birds intimately intertwined with humans. Pigeons were domesticated ~5000–10 000 years ago [26]. Evidence indicating the degree to which pigeons were consumed at funerary feasts and offered at religious ceremonies, such as

FIGURE 2 a) Traditional drying of hay in a barn; b) modern methods of drying hay. Reproduced with permission a) Chris Boese on Unsplash, b) Ruud Morijn on Dreamstime.com.

5237 flocks of pigeons offered by King Ramses II to the priests of the god Amon of Thebes, suggests ancient Egyptians were adept at domestic pigeon husbandry [27].

Greek (Aristotle) and Roman (Pliny the Elder, Varro) historians described the importance of maintaining adequate avian husbandry conditions, but are silent on diseases either in birds or in humans who work with them [28–30]. Neither Hippocrates (460–370 BC) nor Galen (129–?216 AD) warned of bird-related illness; on the contrary, both recommended the use of pigeon excrement in the treatment of open wounds [31].

From the late 14th to the 16th century, as Spanish explorers set out to conquer the world, they brought back many exotic birds that later would be prominent in bird-related HP. After Spain conquered and claimed the eponymous Canary Islands in 1500, the canary trade boomed. In the 16th century, canaries were bred mostly by Spanish monasteries and traded with Italy and Switzerland, and subsequently Germany, Britain and Russia [32]. Parrots and parakeets were imported as pets in 1504 by King Henry VIII for himself and others, although evidence suggests that African parrots were kept as pets in Greece from at least 400 BC [33]. Even the British royal family (queens Elizabeth I, Victoria and Elizabeth II) and the scientist Charles Darwin partook in bird breeding [34]. Moreover, in the 18th and 19th centuries, pigeons became important messengers in the delivery of war intelligence.

In the years that followed Reed's initial 1965 description, bird exposure would become one of the exposures most commonly associated with HP, accounting for up to a third of HP patients [2]. We now understand that bird antigens are not only derived from intestinal mucin present in the bird droppings of many species, but also bird bloom, produced specifically by "powder-down" birds (pigeons, parrots, ducks and budgerigars). Powder-down feathers grow throughout the life of the bird, and their barbules continually disintegrate into a fine powder which the birds use for cleaning and which gives the plumage a characteristic bloom [35]. Exposure to these feathers from close proximity to the bird's environment (bird husbandry) or through feather products (especially feather bedding [36]) increases the risk of HP.

In addition, fungi found in bird droppings or in the bird's environment for these and other bird species may be causative factors in HP, but, just as importantly may also be causative in fungal infection. Bird dropping-associated fungal infections prominently include aspergillus and histoplasmosis. Indeed, fungal infection, not HP, was the initial occupational and environmental ILD associated with birds. The causative agents identified were both linked to pigeons, initially aspergillus in the latter part of the 19th century, and later, in the first half of the twentieth, histoplasmosis. The example of aspergillus is particularly illustrative. Its emergence is attributable to two linked factors: waves of aspergillus-infected pigeons being traded on an international scale and an inter-related practice, particular to the French marketplace, of force-feeding pigeons for greater consumer appeal. The specific technique used was (human) mouth-to-beak administration, a practice that led to aspergillus mouth lesions as well as indolent lung disease with clinical and microbiological findings of pulmonary aspergillus infection. This lung condition, decades before Reed's description of HP, came to be called "pigeon fancier's disease" (a misnomer referring to infection, not HP, and leading to later confusion in nosology) [37].

In the early 20th century, a new form of pulmonary mycosis came to be recognised, in this case histoplasmosis. Initially described by Darling in 1905, from the late 1930s through the 1940s a series of outbreaks were documented in farming families, in military recruits and in various construction activities, in particular demolition. The clearest factor linked to some of the largest outbreaks was exposure to pigeon excreta [38].

Of course, the possibility cannot be excluded entirely that, within the groups of patients with presumed histoplasmosis, there may have been sporadic cases of missed HP. For example, detailed analysis of a cohort of workers in a 1947 disease outbreak in Cincinnati, Ohio that followed shovelling pigeon excreta, identified some with atypical radiographic findings for histoplasmosis (a diffuse miliary pattern, but no hilar involvement) and in some, persistent radiographic changes unaccompanied by the nodular calcifications commonly seen in histoplasmosis. Moreover, pathological examination of the lung lesions in one case demonstrated Langerhans' giant cells (common to both histoplasmosis and HP), but was negative for histoplasma using Baur's stain [39]. Nonetheless, there is no basis to argue that what was called "pigeon fancier's disease", prior to 1965, was actually HP. The case series by Reed *et al.* [25] in 1965 was careful to report that these patients tested negative for histoplasmosis as well as other infectious agents. The pattern of clinical features associated with exposure and mitigated by avoidance, and the response to corticosteroids, suggests an immunological hypersensitivity rather than disease of infectious aetiology. Moreover, at the time, Reed *et al.* [25] highlighted the similarities in his cases to reported accounts of farmer's lung.

Since the initial descriptions of HP in the 1930s, a pattern of causative antigens with similar properties began to emerge. Beyond birds, the most common causative agents have included fungi (*Aspergillus*, *Trichosporon*) and bacteria from the Actinomycetes family (*e.g. Saccharopolyspora* in farmer's lung). *Actinomyces*, literally meaning "ray fungus", was initially incorrectly classified as a fungus owing to its filamentous appearance [40]. Beyond fungi and fungi-like bacteria, mycobacterium species also have antigenic properties sufficient to cause HP, possibly related to their propensity to cause granulomas [41]. In contradistinction to avian HP, which has been convincingly documented as arising from multiple species, HP attributed to mammalian species has been uncommonly and unconvincingly reported [42, 43].

Furthermore, the post-World War II industrial boom augmented our exposure to these immunogenic antigens. Specifically, changes in the way we live brought an increased risk of fungi into the home environment. The replacement of lathe and plaster with the use of drywall (also known as plasterboard, consisting of gypsum sandwiched between two paperboards) in home construction increased in the post-World War II housing boom due to its noncombustible nature and low cost. However, mould was far less likely to grow on nonporous clay-based plaster compared to currently used cellulose-based materials such as drywall [44].

Other indoor technologies promoting HP emerged in the 20th century. In the 1930s, electric-powered fans became much more affordable and, together with damp burlap, blankets or wood shavings (excelsior), the use of evaporative coolers exploded in low-humidity areas of the United States, hence the term "desert cooler", or "swamp cooler" from the fungal and algae-producing aroma akin to a swamp [45]. Similar systems, termed "air coolers" were devised in other countries, such as India [46]. By the 1970s, there were reports of HP due to evaporative coolers, home humidifiers and air conditioning systems containing *Actinomyces* and other moulds previously linked to the development of HP [47].

As yet another example of an emerging fungal-related HP, the first 42 cases of so-called "new-type" summer-type hypersensitivity pneumonitis were first described in 1980 by the Japanese Ministry of Welfare [48]. Summer-type HP is caused specifically by *Trichosporon* spp. which thrive in old wooden buildings in rainy seasons followed by hot, humid summers [49].

Although *Trichosporon* moulds are endemic and causative of opportunistic infections throughout the world, for reasons which are not clear, summer-type HP (or *Trichosporon*-associated HP by any other name) has been reported exclusively in Japan and, even there, only beginning in the latter decades of the 20th century. This could be due to optimal conditions for *Trichosporon* spp. growth, as well as diagnostic bias due to greater clinical awareness and wider availability of *Trichosporon*-specific serum antibodies in Japan.

Beyond fungi and fungi-like bacteria, mycobacterium species also have antigenic properties sufficient to cause HP, as noted previously. Hot water and thermal baths have been popular for millennia. However, it was the manufacture of the modern acrylic and polyvinyl hot tubs and spas in the 1970s and 1980s and the addition of antimicrobial chemicals coupled with the reduction of water exchanges that led to the selective growth of mycobacterium species. By 1986, the first published report of hot-tub lung appeared [50].

Industrial revolutions; industrial disease evolution

As industrial practices evolved, so too did novel patterns of exposures contributing to HP. The evolution in manufacturing during post-World War II industrialisation resulted in new exposures and irritants. The large-scale use of isocyanates in the manufacture of polyurethane resins for flexible foam, synthetic rubber, adhesives and paints was a post-World War II phenomenon. By the 1950s and 1960s, isocyanate vapours were a known pulmonary irritant and then recognised as a cause of new-onset asthma; in the late 1960s, cases of consolidative and pleural lung disease were reported [51], and, in 1976, a case series of four patients with isocyanate-associated HP was described [52]. Asthma remains the primary adverse respiratory health effect of concern in isocyanate exposure, with HP a relatively uncommon adverse effect.

As post-World War II industrialisation increased the use of mechanisation, so too did it increase the use of metalworking fluids. A wide range of metalworking fluids are used to cool and lubricate in various applications with various properties and chemical compositions. In the early 19th century, metalworking fluids contained mostly mineral oil based hydrocarbons or natural greases, later evolving to the addition of emulsifiers and water (so called soluble oils). Since the 1970s, water-based synthetic and semi-synthetic metal working fluids have been increasingly utilised, some with the addition of biocides that reduce some bacterial species growth, but selectively promote others, including *Pseudomonas* spp. Such metalworking

contaminants, recirculated and aerosolised under high pressure, caused the first described outbreaks in the 1990s, termed "machine operator's lung" [53].

Other new exposures continue to be suspected as causative factors in the development of HP. Central to their identification are a pattern as consistently described in the literature; symptom onset when in the presence of an exposure; improvement with avoidance; recurrence upon inhalational rechallenge; typical radiographic imaging, histopathological findings and, in some reports, positive precipitins [54]. As occupational and unsalaried avocational practices evolve, the application of these criteria gives rise to an ever-expanding list of HP-inducing risk factors, including three-dimensional printers (thought to be due to nylon powder used in its manufacture) [55], contaminated home continuous positive airway pressure machines [56] and dental products (methyl acrylates affecting dental technicians) [57].

HP as a "new" pathological entity: we look for what we know

If contributory exposures have been present for centuries, and yet HP only far more recently first described, is it our recognition of pathological patterns that has evolved? The recognition of certain other ILDs as their own distinct entities also did not arise until the early 20th century. In the 1930s, for example, Hamman and Rich [58] presented a collection of patients with an "acute diffuse interstitial fibrosis of the lung", considered to be the first description of idiopathic pulmonary fibrosis (IPF) (now more consistent with acute interstitial pneumonia). They described "an extraordinary and progressive proliferation of fibroblasts within the walls of the alveoli [causing] acute diffuse interstitial fibrosis of the lung" [58]. Following their case series, several other necroscopy reports with similar findings followed [59, 60]. In the late 1950s and early 1960s, several case series of findings from surgical lung biopsies demonstrated that this could be studied ante-mortem, leading to a greater understanding of this pathology [61, 62].

After Hamman and Rich's initial descriptions, in the late 1960s, Liebow and Carrington [63] described different pathological subgroups of fibrosing lung disease, reflecting the expected clinical course, prognosis and known associated conditions. Initially these included "usual" interstitial pneumonia, bronchiolitis interstitial pneumonia, desquamative interstitial pneumonia, lymphoid interstitial pneumonia and giant cell interstitial pneumonia, subsequently revised to add nonspecific interstitial pneumonia, respiratory bronchiolitis-associated ILD and acute interstitial pneumonia [63].

Although hints at a fibrotic lung disease process describing a "fibroid metamorphosis" in chronic pneumonia and "cirrhosis of the lung" were reported previously by William Fox and Charles Bastian in 1871 and William Osler in 1892 [64, 65], their accompanying descriptions of "often unilateral disease [which] seldom occurs except in the presence of tubercles" [65] suggests chronic pneumonia as a sequela to suppurative and tuberculous lung disease, which would have been seen far more commonly during this time [64, 65].

Clinicopathological descriptions of patients with inorganic dust diseases from mining, stone masonry and grinding resulting in pulmonary fibrosis were more common in the late 19th century literature, again differing from what we would now consider ILD. It is noteworthy that Greenhow [66], in 1870, described a case and subsequent post-mortem of a nacre (pearl shell) worker from Birmingham, England. Pearl shell is a known, albeit rare, exposure associated with HP [67], and one that does not fit easily within the bird–fungus–bacterial grouping. Greenhow's early report, with its description of "lamellated fibrous nodules" [66], was a case more in keeping with mixed dust fibrosis such as that seen in miners or coal workers. Perhaps we do not see what we do not know.

Although Fawcitt [9] described several post-mortems with fibrosis (figure 2 therein), it was not until the 1950s/1960s that granulomas or "sarcoid-like lesions" accompanied by interstitial pneumonitis and subsequent fibrosis as manifestations of HP were described [21, 68, 69]. Finally, in 1982, the current histologic hallmarks of diagnosis were outlined in a series of 60 patients with clinically verified farmer's lung: lymphocytic interstitial inflammation, granulomas and organising pneumonia [70]. Thus, the lack of established pathologic criteria for HP may have limited the wider recognition of this entity until the second half of the 20th century. In addition, the marked heterogeneity in confirmed and suspected causes of HP may be a factor that has led to diagnostic confusion. Even now, failure to explore the clinical history for HP exposures, or obtaining only limited diagnostic material, may lead the clinician to erroneously classify the diagnosis as IPF or another ILD, rather than HP [71]. Furthermore, changing terminology over time tends to obfuscate matters. The earlier meaning of "bird fancier's lung" applied to mycosis is one example; the generic use of "mouldy" in the past literature to describe any contaminated agricultural product, whether by true mould or by bacterial species, is another. A related phenomenon has been the tendency of authors to coin colourful, one-off monikers for each new HP syndrome.

In the past several decades, our conceptualisation of HP has been shaped not only by a greater understanding of pathology, but also by emerging imaging technologies. The increasing use of chest radiographs from the 1920s and then computed tomographic scanning from the early 1980s has not only provided a greater understanding of the disease processes without reliance on pathological specimens, but has also aided in the diagnosis of individual cases and the ability to characterise clinicopathological patterns in larger series of patients, differentiating HP from other ILDs, and within HP, between acute and chronic forms [72–75]. Indeed, radiographic diagnostics arguably comprises the single most important factor in 20th century recognition of HP.

Other technological and scientific advances in microscopy, bioassays and computational genomics and transcriptomics have yielded mechanistic insights into the inflammatory and fibrotic pathways that may contribute to HP [76]. This has led to the identification of potential immunomodulatory risk factors beyond the causal exposure itself, including the effect of previous respiratory infections (Epstein–Barr virus, human herpesvirus 7 and 8, cytomegalovirus, parvovirus 19 [77]), pesticide use in farmers [78], the potential mechanism of smoking inhibition of HP [79] and the role of genetic variants, including human leukocyte antigen [80], mucin 5b gain-of-function variants and protein-altering telomere-related gene variants [76]. The insights gained from all of these emerging tools and techniques are potentially valuable, but enriched even further when contextualised in an understanding the history of HP. That history makes clear that changing concepts of HP over time have shaped how clinicians have identified, managed and attempted to prevent this challenging condition.

Conclusion

A careful examination of the historical record suggests that, despite causative exposures being present from prior decades or even centuries, the recognition of HP as a distinct entity is a rather recent phenomenon. Milestones marking that history are summarised in table 1. The historical perspective reflected in the text and in table 1 is based on the results of the snowball searching strategy supplementing utilisation of standard biomedical databases and further integrating additional critical review of selected historic texts. Nonetheless, we acknowledge that additional relevant examples may have been missed.

Whilst the lack of medical imaging and other diagnostic modalities prior to the early 1900s may have led physicians to conclude that such cases had alternative diagnoses, such as asthma, bronchitis, tuberculosis, mycosis or even mixed-dust fibrosis, it is also possible that other factors have led to emergence of HP in the modern era. A common historical thread appears to be changing technologies and other occupational and indoor living factors that introduced new or more intense exposures or, occasionally, reduced or eliminated previously implicated exposures. History can teach us much about HP, but there is still much to be learned.

TABLE 1 Milestones in the history of hypersensitivity pneumonitis (HP)

Year	Authors [reference]	Comments
1700	Ramazzini [6]	Refers to respiratory symptoms in grain workers, but without characteristics that would indicate an HP-like condition (asthma more likely)
1879	Greenhow [66]	Lung pathology in a shell worker, but more consistent with pneumoconiosis than nacre HP
1895	Renon [37]	Pigeon handler's disease first associated with mould, but caused by active infection, not a hypersensitivity response
1932	Campbell [8]	Initial HP clinical series reported on farmer's lung
1932	Towey *et al.* [11]	HP reported due to spore-forming bacteria in bark (maple bark stripping in railroad tie manufacturing)
1941	Jamison and Hopkins [13]	Initial report of bagassosis, outbreak related to a new manufacturing process
1955	Cancella [16]	Suberosis, HP in cork workers, reported
1958	Dickie and Rankin [21]	Initial pathologic descriptive term "poorly formed granuloma" as a hallmark of HP
1963	Pepys *et al.* [22]	Actinomycetes identified as causal in farmer's lung
1965	Reed *et al.* [25]	Initial clinical report of pigeon breeder's HP
1970	Banaszak *et al.* [47]	HP related to air coolers and air conditioners described
1976	Charles *et al.* [52]	Isocyanate-caused HP initially reported
1980	Murao *et al.* [48]	Summer-type HP initially described in Japan
1986	Jacobs *et al.* [50]	Hot-tub HP first reported
1989	Silver *et al.* [72]	CT use with radiological and pathological descriptions of HP
1995	Bernstein *et al.* [53]	Metal cooling fluid-caused HP identified

CT: computed tomography.

Suffice to say, exposures not previously known to cause HP will continue to be discovered over time. Looking to the past, as well as vigilance going forward, can help us mitigate HP risk in future years.

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