

Historical Perspective

From the Definition of Silicosis at the 1930 Johannesburg Conference to the Blurred Boundaries Between Pneumoconioses, Sarcoidosis, and Pulmonary Alveolar Proteinosis (PAP)

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The 1930 International Labour Office Conference on silicosis in Johannesburg identified silicosis by setting a medicolegal framework to its nosology: as with other occupational illnesses, its medical content was fixed under economic pressure. This article follows a reading of all the proceedings of this conference (debates and reports of experts) to examine their potential impact on the etiology and nosology of other diseases, specifically sarcoidosis and pulmonary alveolar proteinosis (PAP), “idiopathic” diseases in which inorganic particles may be involved. We propose renewed study of the role of inorganic particles in these diseases. To do this, we propose to mobilize detection means such as mineralogical analysis and electron microscopy and in depth interviewing that are currently seldom used in France, in order to establish diagnosis and the potential occupational and environmental origin of these diseases. Am. J. Ind. Med. 58:S31–S38, 2015. © 2015 Wiley Periodicals, Inc.

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INTRODUCTION

Since the twentieth century, the leading causes of illness have been attributed to nutritional deficiencies, to exposure to toxic substances and infectious agents, to psychological dysfunction, and/or to genetic predisposition [Genuis, 2012]. A review of the 1930 International Labour Office Conference on silicosis in Johannesburg proceedings [ILO, 1930] opens the way for new avenues of research on possible environmental causes of diseases that are considered to be of undetermined etiology. We concentrate here on sarcoidosis and acute pulmonary alveolar proteinosis (PAP) [Blanc, 2015] to show how these idiopathic diseases may be revisited from an understanding of silica-induced lung pathologies as expressed by the 1930 Johannesburg Conference.

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This paper is less historical than medical. As opposed to the historical method, it re-examines historical material with contemporary medical questions and methods. This is not to put into question the role of the participants of the 1930 Conference, but to highlight how the reading of the 1930 proceedings may inspire current medical research. We will first show to what extent the nosological framing of silicosis designed by this Conference is, seen with today's eyes, restrictive despite the conference's pioneering view on particle toxicity. It will enable us to suggest a historical hypothesis about the nosological and etiological consequences that this approach has generated for other possible dust hazards, especially in relation to sarcoidosis and acute silico-PAP. We further suggest that under-identification of silica role's was due to technological constraints, as seen with today's eyes. From there, we will propose a new approach of detection that could help test scientific hypotheses and which will hopefully build a body of evidence on possible environmental causes of sarcoidosis and PAP.

HOW THE 1930 JOHANNESBURG CONFERENCE CAME TO A RESTRICTIVE NOSOLOGICAL DEFINITION OF SILICOSIS

Topics covered in the reports of experts from the nine countries participating in the Conference and discussed at the meeting indicate varying areas of interest but it is quite obvious that the opinions of South African experts and their expertise on the subject predominate. The result is an almost exclusive interest in mining activity: 52% of the 585 pages of the main report are on the mines of the Witwatersrand. The preponderance of mining issues also features in the Australian report, unlike the Dutch report, which deals exclusively with stone work (excluding mining). The British, American and German experts, however, seem to have been interested in a wide range of occupations. Whereas Belgium (whose delegate was absent) submitted a short report, the Italians and Canadians evoked the problem of exposure to asbestos. In the final resolutions of the Conference, there was no mention of the diversity of occupations likely to be exposed to silica. All in all, therefore, both in the reports and in the debates the interest in mining activities largely prevailed.

This feature can be understood given the economic context and goals of the conference which included assessing to what extent a definition of disability in miners could be combined with maintaining productivity. The South African delegates, for whom mining was economically crucial, sought a definition of silicotic disease compatible with a "minimalist" recognition, at lower cost, and consistent with their approach to the (racial) management of labour.

Some Medical Restrictions or Dead Ends *A clinical and radiological confusion between "closed tuberculosis" and acute silico-PAP*

According to the terminology used in South African legislation, "tuberculosis means tuberculosis of the lungs or of the respiratory organs" and is deemed to be present wherever it is found by the Bureau "either (a) that such person is expectorating the tubercle bacillus, or (b) that such person has *closed tuberculosis* to such a degree as seriously to impair his working capacity and render prohibition of his working underground advisable in the interest of his health" [Gardner et al., Resolutions adopted by the Silicosis Conference, p. 22, in ILO, 1930](emphases added).

Thus was the notion of "closed tuberculosis" stated. Tuberculosis was identifiable, inter alia, by rapid radiological aggravation associated with general symptoms (fever, weight loss, asthenia) impairing the ability to work, but without the systematic examination for *Mycobacterium tuberculosis* in sputum. Our hypothesis is that acute silicosis, with a PAP reaction which may be characterized by the same clinical and radiological signs, could thus have been labeled as "closed tuberculosis"¹.

The truncated pathological definition of silicosis

Our historical hypothesis is that the final pathological definition of silicosis was truncated according to economic interests.

Ultimately, silicosis was defined on the basis of discussions that, initially considered, could just as well have produced a broader notion of the disease. Two early stages showing inflammatory reactions to inhalation of dust were identified: bronchiolitis and the accumulation of phagocytes containing dust in the pulmonary lymphoid tissue. At the Lyon Conference of 1929 (Piedelièvre, 1929), the second stage was assimilated by Mavrogodato to a pseudo-tuberculosis granuloma (that is to say a granulomatous reaction with epithelioid and gigante-cellular reaction). At the 1930 Conference, these first two stages of the disease were excluded from the final definition of silicosis disease:

"The conditions described above under a) and b) do not constitute the disease silicosis." [Gardner et al., Resolutions adopted by the Silicosis Conference, p. 4, ILO, 1930].

¹ It may be recalled here that well before 1930, Thomas B. Peacock [Greenberg, 1992] had laid the foundations of a reflection on the relationship between exposure to dust, tuberculosis and silicosis [Peacock, 1860], using the term "phthisis" in a broad sense.

Silicosis was thus considered to be present only from the third stage of the pathological changes: that of the silicotic nodule [Rosental, 2015].

The exclusion of acute silicosis with PAP

Text in the proceedings from Middleton shows that silico-PAP was identified in presentations to the conference:

“Case II - Died 4 June, 1928 aged 17, female [...]. Post-mortem examination: the findings closely resembled those described in case I. Microscopic examination of the lungs showed numerous large fibrotic patches surrounded by small cell infiltration, and in the interstices were finely granular pigmented or black deposits. The alveolar tissue was much reduced; the walls were thickened with fibrous tissue and the alveoli were filled with albuminous exudate. The general picture was that of chronic inflammation with fibrosis. The glands appeared to be almost completely fibrosed. There was no evidence of tuberculosis and tubercle bacilli were not seen” [Middleton, in ILO, 1930, p. 476].

The description of acute silicosis with PAP in factories manufacturing scouring powder was in fact contemporary to the 1930 conference [Middleton, 1929]. In all, four cases of early deaths were presented at the conference, two of which had radiological aspects of miliary tuberculosis with negative *Mycobacterium tuberculosis* research in sputum.

However the participants at the 1930 conference did not include acute silicosis with PAP in their conclusions of the anatomopathological findings of the conference.

A PIONEERING VIEW ON PARTICLE TOXICITY

In this area as in others, the 1930 Johannesburg Conference systematized existing observations. From the 19th century, Thomas B. Peacock [Peacock, 1861, Peacock, 1865], a pioneer of industrial and environmental hygiene, had endeavored to distinguish, from a mineralogical point of view, the role of silica from that of other dust in lung diseases [Greenberg, 1992]. The 1930 Conference showed a particular interest in the matter. It tried to define the physiopathologic mechanisms of dust, and notably silica, on the lung.

“From the information supplied by various members, the disease becomes noticeable after differing periods of exposure to siliceous dust depending, apparently, upon: (a) the amount of dust inhaled; (b) the percentage of free silica contained therein, (c) the size-frequency (or fineness) of the particles inhaled.” [Loriga et al., Resolutions adopted by the Silicosis Conference: Report of the Sub-Committee on Preventive Measures, p. 13, in ILO, 1930].

Free silica in the air (not the chemically combined form of silicate) was then classified under a long list of names, e.g.

quartz, flint, slate, quartzite, quartzose, sand, free silicic acid, and silica colloid, which illustrated the diverse background of the delegates who were present in Johannesburg; clinicians, hygienists, pathologists, work doctors, and mining engineers.

According to these delegates, the toxicity of mineral dust depended on:

- The dose, from which the establishment of an exposure limit values may be inferred, work in humid environments and the use of protective equipment [Ferguson and Scott, in ILO, 1930, p. 162].
- The mixing of particles: “other dusts simultaneously with silica might affect the development of silicosis” [Loriga et al., Resolutions adopted by the Silicosis Conference: Report of the Sub-Committee on Preventive Measures, p. 14, in ILO, 1930]. The occurrence of silicosis may thus vary depending on work environment. The argument here is that the presence of other particles can increase or decrease the toxicity of silica, either by reducing its inhalation or by facilitating its evacuation by the lungs.
- The size of particles and their exchange surface area within the tissues. To support the idea that the toxicity of particles increases as their size decreases, the speakers used the concept of “solubility”: i.e. that silicic acid released from the surface of silica is the toxic component. Solubility of silica and exchange area were held to be crucial pathogenic factors in silicosis. Furthermore, the possibility that silica particles may be unobservable because of their small size, and this even under polarized light, was well known [Strachan and Simson, in ILO, 1930, p. 228].

ADVANCES IN TECHNIQUES AND KNOWLEDGE SINCE THE 1930s

Among the experts of this assembly were specialists in observation instruments, united by their technical competence on the subject [Melling and Sellers, 2012]. Given that the point of view of delegates was influenced by the techniques available we review here the issues which were addressed in 1930, and subsequently, as technical resources and knowledge evolved. Based on these advances, we propose the hypothesis of the possible role of inorganic particles, including silica pulmonary overload, in sarcoidosis and PAP.

Diverse and New Detection Instruments

Since 1930, clinical examination of data has not changed, but complementary lung explorations have developed considerably. Radiography has been used systematically in

the monitoring of high-risk occupations and tuberculosis. In the 1950s, tomography improved radiological investigation and was later replaced by thoracic computed tomography (CT) scanning in the mid-1970s. This has provided additional information, both for early diagnosis of disease as well as for identifying complications [Begin et al., 1991; Jun et al., 2013]. Recently, the positron emission tomography (PET) scan has enabled medical investigators to obtain previously undetectable information on the inflammatory or tumoral nature of observed lesions [Schuster, 1989].

Moreover, current flexible endoscopy techniques enable pulmonologists to capitalize on the practice of endoscopic examination for early pathological studies such as bronchial or transbronchial biopsies and cytology studies of bronchoalveolar lavage [Reynolds, 1987]. Thoracic surgery and anesthesia facilitate tissue sampling. Thus, it is rare not to be able to obtain cytological or anatomopathological analysis of suspicious lung lesions, which was not the case in the 1930s.

Finally, pulmonary function tests measuring different lung volumes were first widely used in the 1950s in the framework of clinical and epidemiological studies. These have become an indispensable tool for medicolegal compensation.

The Potential Contribution of Electron Microscopy Combined With Mineralogical Analysis in a Context of Growing Interest in Nanotoxicology

Methods determining elements and their crystallographic arrangement have been considerably developed since 1930, of which some were then quite unknown. The chemical composition of dust could be assessed in 1930, but crystal structures were difficult to determine. Currently, X-ray diffraction, infrared, and mass spectrometry and electron microscopy allow medical investigators to perform a more complete analysis of mineral particles at a microscopic and nanoscopic level.

Mineralogical analysis of digested and filtered lung tissue can now be used to count asbestos bodies, for example [De Vuyst et al., 1998; Vincent et al., 2011]. The proof of the concept of the relationship between the level of dust inhalation and various types of lung disease caused by asbestos has thus been demonstrated and has resulted in standardized criteria for correlating exposure with disease [Henderson et al., 2004].

The same procedures (including bronchoalveolar lavage (BAL) [Nugent et al., 1989; Gibbs and Pooley, 1996; Vincent et al., 1995; Catinon et al., 2014] also allow the observation of non fibrous particles that digital image analysis techniques can then count [Abramoff, 2004]. Combined with these, transmission electron microscopy (TEM) or scanning electronic microscopy (SEM) make it possible to observe particles

smaller than 400 nm and smaller than 100 nm when they are in clusters. As for microanalysis (MA), it is used to identify the nature of the constituent atoms, while X-ray diffraction provides information on their crystalline characteristics. However, these examination techniques are rarely performed in France, even for asbestos body tests that can be reimbursed by the general system of health insurance. These examinations, which are still expensive for non-fibrous particles, require specialized equipment and experts in medicine, chemistry, and mineralogy to work together in a single team.

Consistent with the assertions made in Johannesburg in 1930 about the importance of particle size, nanotoxicology is now a booming field of research [Seaton and Donaldson, 2005; Seaton et al., 2010]. The same mass of inhaled particles can produce toxicity ranging from 1 to 1000 according to whether their size is coarse or fine [Oberdörster et al., 2005]. The toxicity of nanoparticles of crystalline or amorphous silica, which is related both to their size and dose, is directly related to an increase in free radicals. Silica can cause a granulomatous inflammation, as may be the case for sarcoidosis, without developing into fibrosis, and such inflammation could even be reversible according to the results obtained from experiments carried out on animals [Napierska et al., 2010].

DISCUSSION: FROM THE 1930 SILICOSIS TO SARCOIDOSIS AND PAP TODAY

If we look at the concepts of granuloma formation and closed tuberculosis, on the basis of all the medical detection techniques which have been developed since, we can see that the conclusions reached in 1930 led to a narrow definition of silicosis and silica related disease. Specifically, the choices which were made, based on the considerations of the era, contributed to dissociating the etiology of PAP or sarcoidosis from exposure to inorganic dust.

However, other exploration techniques can now be used to verify the extent to which exposure to these dusts may cause lesions in healthy tissue.

The Importance of an In-Depth Interview

We have previously described four clinical cases which underscore the need for an in depth interview in accurate diagnosis.

In two of the cases of acute silicosis [Dumontet et al., 1991a,b; Vincent et al., 1995], the interview and the dialogue between the clinician and anatomopathologist proved to be essential. In the first case, while the radio-clinical evaluation had initially suggested sarcoidosis, the pathologist who examined the biopsy had established a diagnosis of lipidosis. Only by repeating the patient's interview did it emerge that

the patient had been sniffing scouring powder, a product rich in quasi-pure silica dust at that time. The patient's case then evolved into Sharp's syndrome [Vincent et al., 1996]. In the second case, the patient had first denied such exposure. But when she was re-interviewed after the biopsy which showed a reaction to foreign body, she admitted, on condition that it was kept secret from her family, that she also regularly sniffed scouring powder.

Two other cases of granulomatous disease linked to inorganic exposure illustrate why it might be important to ask patients about possible applications of mineral powders on abraded skin areas [Vincent et al., 2004] or about hobbies such as DIY [Catinon et al., 2014].

The Importance of Mineralogical Analysis

Polarized light microscopy study

In the two cases of acute silicosis mentioned above, the biopsies had not been examined under polarized light at first. The guided re-interview alone convinced doctors of the need to use polarized light, which revealed many birefringent particles in the alveolar proteinosis. In his initial description of "idiopathic" PAP, Rosen did not mention the research on silicoproteinosis among scouring powder baggers [Rosen et al., 1958]. But he mentioned many other trades exposed to mineral dust, where polarized light often revealed birefringent particles in the lesions. Indeed silicate particles as talc, clay, kaolin have a stronger bi-refringence than silica. However, he did not posit a clear causal relationship between these particles and the disease. Forty years later, in the ACCESS study of sarcoidosis [Access Research group, 1999], the search for particles under polarized light in granuloma was not mentioned as systematic. Similarly, in a French retrospective study [Vincent et al., 2006] of 47 cases of sarcoidosis, polarized light studies were only mentioned in 38% of the cases. These observations lead us to believe that the non-systematic use of polarized light may contribute to the underestimation of the role of inorganic dust in association with such diseases as PAP and sarcoidosis [Catinon et al., 2014]. Of course, the causal link between the presence of birefringent particles and the onset of disease cannot be established from co-occurrence. But these particles are certainly under-detected today, making it difficult to verify a possible "particle-disease" co-occurrence.

The use of other mineralogical analysis techniques

Abraham [Abraham and McEuen, 1986] showed that most of the 24 PAP cases they studied under optical and scanning electron microscopy (EM) and microanalysis (MA) were associated with an overload of small, inorganic

particles of different types. They did not refer to the cases of acute silicosis with PAP from scouring powder from the 1930s, or to the possibility of a causal relationship between this overload and PAP. In the 1990s, idiopathic PAP was considered to be an autoimmune disease with anti-GMCSF antibodies [Dranoff et al., 1994]. Consequently, in their *New England Journal of Medicine* overview of the mechanisms of PAP, Trapnell et al. [2003] rejected the causal "mineral overload" theory, arguing that it was impossible to "find such agents in the lung biopsy samples of most patients". Their conclusion thus contradicted that of Abraham, whose work Trapnell et al. did not cite.

The recent study of diseases resulting from exposure to indium [Cummings et al., 2012] involves EM and MA techniques, bringing to the forefront once again the hypothesis that PAP may be associated with exposure to inorganic agents [Costabel and Nakata, 2010]. The same applies to sarcoidosis, for which the triggering role of inorganic particles has been invoked [Gentry et al., 1955; Comstock and Keltz, 1961; Rafnsson et al., 1998; Jajosky, 1998; Vincent and Lievre, 2002; Newman and Newman, 2012], especially since the "mini-epidemic" of this disease among workers who cleared the rubble from the World Trade Center [Jordan et al., 2011; Crowley et al., 2011]. A cluster of this granulomatous disease from exposure to silica nanoparticles [Song et al., 2011] has been described using EM and MA.

Underestimation of the Role of Inorganic Dust in "Idiopathic" Disease

Our hypothesis, based on a reading of discussions from the 1930 Johannesburg conference, is thus that the truncation of silicosis may have limited the awareness of the medical field to acute diseases such as alveolar proteinosis as well as of incipient chronic granulomatous diseases. The Conference shaped an approach that de facto obscured the range of possible associations between exposure to inorganic particles and a wide array of diseases [Fleck, 1981; Rosner and Markowitz, 2005; Rosental et al., 2009]; at the very least, it slowed the development of research on these associations, and agreement on their results. Others examples may be found with scleroderma, lupus and polyarthritis [Koeger et al., 1995; Hausteiner and Andereg, 1998; Parks and Cooper 2005].

Additionally, silica is nowadays considered as inflammatory and fibrosing, and is classified as a carcinogen at the same level as asbestos by the IARC [IARC, 2012]. Silica nanoparticles can cause granuloma, which are sometimes reversible if exposure is interrupted, but which can also develop into fibrosis. Occupational exposure to silica is most certainly underestimated or overlooked, as was—and still may be—the case for exposure to asbestos. The under-detection of occupational factors involved in these diseases is widespread, but the ubiquity (and paradoxically "invisibility") of silica in

industrial processes is conducive to underestimation [Nij et al., 2003].

In addition, questionnaires are sometimes incomplete. Thus, the questionnaire developed by the Société de Pneumologie de langue Française (French Language Society of Pulmonology) and the Société Française de Médecine du Travail (French Society of Occupational Medicine) do not cover exposure to silica in agriculture [Dalphin, 2002]. Similarly, it is regrettable that the ACCESS Study [Newman et al., 2004] on sarcoidosis did not examine the agricultural trades, where the handling of pesticides may be masking exposure to silica. This characteristic omission of the agricultural sector appears to be detrimental, judging by Archer's study [Archer et al., 2002] of 24 farmers showing levels of exposure to silica much higher than OELs. Likewise, using a questionnaire that specifically focused on exposure to silica, Parks and Cooper [2005] identified odds ratios as high as four for lupus associated with such exposure.

We believe there is need to develop studies that can correlate a targeted interview [Cavalin et al., 2013] with the results of a metrological air dosage and a mineralogical analysis of lung tissue or of BAL, in order to thoroughly test the hypothesis of an association between inflammatory, fibrous and/or autoimmune diseases [Miller et al., 2012] and an overload of silica or other inorganic particles.

This correlation is the aim of a case-control study being conducted by the mineralogical analysis laboratory from the Saint Joseph and Saint Luc Hospital in Lyon, the Sarcoidosis group from the French Language Society of Pulmonology and the European Research Centre (ERC) Grant Silicosis project led by the Centre d'Etudes Européennes, Sciences Po, Paris, entitled "MINASARC". The study will compare the dust levels from the BAL of 20 healthy subjects and 20 sarcoidosis patients analysed by optical and electronic microscopy and microanalysis after blind coding. These findings will be analysed in relation to a) a questionnaire examining professional and environmental exposure to silica and non-fibrous inorganic particles and b) in situ analysis of granulomatous anatomopathological samples using optical and electron microscopy and microanalysis.

CONCLUSION

The 1930 Johannesburg Conference was a watershed in the international recognition of silicosis. However, constraints linked to ore extraction costs and the strategic economic importance of coal (and of gold for South Africa) led to a "minimalist" definition of silicosis, resulting—this is our hypothesis—in delaying the identification of, or even the search for, links between exposure to silica and various inflammatory diseases, and providing the grounds for the

labeling of acute PAP and sarcoidosis as idiopathic. Advances in lung examination techniques in the following decades were not able to counter this tendency because silicosis was concurrently falling into oblivion in Western countries as mining activity declined.

Our hypothesis remains to be tested in prospective studies pairing a targeted interview on occupational and non-occupational exposure with a mineralogical analysis performed in situ and/or after tissue digestion. Nanoparticle studies showing that silica tends to be associated with non-fibrosing granulomatous inflammatory reactions could corroborate our hypothesis.

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