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Mesothelioma and asbestos, fifty years of evidence: Chris Wagner and the contribution of the Italian occupational medicine community

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Key words

Asbestos; mesothelioma; history

Summary

Background: *One of the first studies that "convincingly" described the relationship between pleural mesothelioma and asbestos was made by Wagner, Sleggs and Marchard in 1960. This article, published fifty years ago, contains much of what we still know to-day about malignant mesothelioma.* **Objectives:** *The aims of this article were to analyze the historical and scientific developments that led to the publication of Wagner's paper, to critically examine its contents and to consider the contribution to the international debate on the carcinogenesis of asbestos fibres made by occupational medicine in Italy in that period.* **Methods:** *A thorough analysis of scientific and historical literature on the relationship between asbestos exposure and tumours was conducted, with special regard to the articles by Italian authors in the 1960's.* **Results:** *The decisive role of Wagner's paper in understanding the aetiopathogenetic mechanisms of asbestos-related tumours is inconfutable. In particular, his article clearly demonstrated the existence of a typical cancer of the mesothelium, expressing three fundamental principles of the epidemiology of occupational cancer: association with the carcinogen, latency and individual susceptibility. Enrico Vigliani, then director of the "Clinica del Lavoro" in Milan, made important contributions to this debate, also through the collection of data regarding mortality among Italian asbestos workers.* **Conclusions:** *Wagner's 1960 paper can be considered as a milestone not only in the history of occupational and environmental health, but also in the evolution of other medical disciplines such as epidemiology, pathology and oncology. A re-appraisal of the Italian contributions to the international debate on this subject should be considered.*

Riassunto

«Mesotelioma ed amianto, cinquanta anni di evidenze: Chris Wagner e il contributo della medicina del lavoro italiana». *Nel 2010 ricorrono i cinquanta anni dalla pubblicazione dell'articolo che in maniera più convincente ha stabilito, a livello internazionale, il rapporto tra mesotelioma pleurico ed esposizione all'amianto. Il lavoro, scritto da un gruppo di medici coordinato dal sudafricano Chris Wagner, contiene numerosi elementi innovativi, sia nel campo della medicina del lavoro, che in quello della patologia, dell'epidemiologia e dell'eziopatogenesi dei tumori*

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correlati a un'esposizione lavorativa e/o ambientale. A proposito del dibattito sul rapporto tra amianto e tumori sviluppato in occasione della pubblicazione dell'articolo di Wagner merita di essere ricordato anche l'importante contributo offerto da parte di autori italiani, in particolare da Enrico Vigliani.

Introduction

In July 1960 the *British Journal of Industrial Medicine* published a paper that rapidly became one of the best known and cited works among specialists in occupational medicine, because of its decisive contribution to the identification of the relationship between asbestos exposure and mesothelioma (25). According to Murray, this article, written by a young and unknown South African PhD student in Pathology, Christopher John (Chris) Wagner (1923-2000), together with the chest specialist Christopher Sleggs and the thoracic surgeon Paul Marchard, "took the scientific world by storm" (13).

The 50th anniversary of this article and the 10th anniversary of Wagner's death provide us with the opportunity of re-reading this study, and comment on its decisive role in improving knowledge on the epidemiological and aetiopathogenetic features of occupational tumours, particularly asbestos-related cancers. In addition, the contributions to the debate on the carcinogenesis of asbestos fibres provided by the Italian scientific community of that period (particularly by Enrico Vigliani, then director of the "Clinica del Lavoro" of Milan), which is often neglected by international historians, were also re-appraised.

Previous state of knowledge

When Wagner wrote his paper, adverse effects had already been described in workers exposed to asbestos fibres. In particular, during the 1920's the first demonstrations that the inhalation of asbestos dusts could result in fibrosis of the lungs (asbestosis) had been provided by several studies, including Italian Authors (4, 16, 19). In 1931 the clinical and radiological surveys conducted on workers exposed to asbestos by medical inspectors of factories in Great Britain led to the "Asbestos Industry Regulations" to control asbestos dust exposure (27). In addition, shortly before Wagner's paper, Richard Doll (1912-2005) had shown a significant increase in the risk of lung cancer among workers exposed to asbestos before the "Asbestos Industry Regulations" came into force (5, 7), confirming what had been suggested by clinical cases described in Europe and the United States in the previous two decades (6, 8, 15). Even if data on the effects of asbestos on the pulmonary parenchyma and *interstitium* were available, the lesions this mineral could cause in the pleural tissue had not been clearly identified. Pleural mesothelioma, first described by a namesake of Wagner, the German pathologist Ernst Leberecht Wagner (1829-1888) at the end of the nineteenth century (21), was so rare (previous studies had collected only a few cases) that many scientists, including the distinguished Australian pathologist Rupert Allan Willis (1898-1980), doubted its existence (25). In 1960 Wagner "convincingly" – through the collection of 33 biopsies and necropsies, the most extensive at that time – demonstrated the pathological autonomy of "primitive" pleural tumour and its association with asbestos, that had been previously postulated by some German pathologists, particularly Hans Wilfrid Wedler, in the early 1940's (17, 26). Actually, the hypothesis postulated by the German scientists, who had also taken further the studies by Doll and Hill on the carcinogenicity of tobacco smoke, were not taken seriously outside Germany. According to Proctor, this lack of consideration was due to "both the conservatism built into post-war epidemiology and the post-war political disregard for all things German, the stigma of Nazism" (17). The science of epidemiology, which was developed in the 1950's, required large numbers of cases which were not available to early asbestos researchers. Thus, some American epidemiologists at the end of 1950's were able to claim there were

"too few cases and too little epidemiological data to established a significant relationship" between asbestos and pleural mesothelioma (17). Therefore, Wagner's work was decisive in clarifying this association.

Clinical and pathological observations in South Africa

As documented by Wagner himself, South Africa was rich in asbestos mines, especially blue asbestos (crocidolite) (25). Its extraction, however, was commercially and economically less profitable than gold and diamonds; this was the reason why workers' health conditions in asbestos mines were not taken into consideration and pulmonary asbestosis was less studied than silicosis. Thus, in 1954 the *South African Government Mining Engineer*, headed by Tony Gibbs, asked the *Pneumoconiosis Research Unit* (PRU) in Johannesburg to examine the problem of occupational diseases in the asbestos fields and verify if South African asbestos could cause the same diseases which had been identified in the Western countries (11). Wagner had begun working at the PRU in 1956 and in the same year he described a case of diffuse pleural mesothelioma submitted for necropsy examination in a Bantu man who was thought to have suffered from tubercular pleurisy. Wagner found occasional clumps of asbestos bodies in the air spaces of the lung of this man (23). In the same period, Christopher (Kit) Sleggs, the superintendant of the *West End Tubercolosis Hospital* in Kimberly, observed that some cases suffering from tubercular pleurisy were inevitably fatal. All the deceased subjects came from the same geographical area, the *Asbestos Mountains area*, west of Kimberly. Assuming that those cases might have developed tumours, Sleggs asked the surgeon Paul Marchard to take open biopsies from any suspected case still alive and to send specimens to Johannesburg for histological assessment (23). In this way, Wagner was able to diagnose a large number of pleural meotheliomas in Sleggs' patients. The increased incidence of an extremely rare tumour, the same geographical origin of all the cases and the asbestos bodies seen by Wagner in the lungs of the first case, led the three physicians to postulate a possible association with asbestos (23). To confirm this hypothesis, an accurate collection was made of the occupational and environmental history of these patients, which revealing past asbestos exposure.

The first results of these observations were presented at the *Pneumoconiosis Conference* held in Johannesburg in 1959. The papers by Sleggs and Wagner were met with great interest and the meeting endorsed the need for further research, which encouraged them to submit a paper on this subject to the *British Journal of Industrial Medicine* (9).

"Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province" (25)

The 12-page article contained 3 tables and 12 figures showing radiological and histological findings. In the introduction the authors stated they had located 33 "histologically proven cases" of pleural mesothelioma (22 men, 11 women, aged 31 to 68), despite the rarity of this tumour in South Africa ("no neoplasm of this nature has been diagnosed amongs 10,000 lungs examined" in a five-year period) (25). In addition, they explained the reasons suggesting asbestos might be implicated in the pathogenesis of the disease. "Asbestos was found in the lungs of the first case" (25) and ten cases were referred from an asbestos mining area; moreover, a detailed investigation regarding past occupation and place of residence had shown asbestos exposure in all but one of the 33 cases. After a detailed historical and geographical description of the "Asbestos Area of the North-West Cape" and the report of the chemical type of the mineral mined throughout that area (mainly crocidolite), the authors meticulously described eight case histories, all supported by histological and radiological pictures, illustrating various aspects of the disease and the different kinds of exposure to asbestos dusts. In the discussion, the authors wanted to demonstrate in the first place, by describing the histological pattern of all the analyzed tumours, the

existence of primary malignant tumours of the pleura, in contrast to those who considered these tumours to be only secondary in origin. The authors then accurately analyzed all the scientific literature on asbestos-related tumours and described all the attempts to reproduce neoplasms in experimental models *in vivo* by exposing animals to asbestos dust.

This thorough review of the scientific literature would have allowed the authors to emphasize their findings but the conclusions were more cautious: "the pathological evidence for associating these tumours with asbestos exposure is not conclusive" (25) and the authors "still regarded the asbestos link as somewhat tenuous" (9). This caution was motivated by the following two considerations. First, only in eight of the thirty-three cases was evidence of asbestos exposure demonstrated, while in the other twenty-four cases only circumstantial evidence of non-occupational [environmental] exposure was found. Secondly, there were no similar cases in the neighbourhood of the Transvaal asbestos mines, where crocidolite and amosite asbestos were also mined. According to McCulloch, the explanation why mesothelioma cases were not identified in the Transvaal is linked to the fact that its communities were very poor and isolated, with little access to medical care, and there were no hospitals or chest specialists, such as Sleggs, to identify cancers amongst asbestos workers and their families, as in Kimberly. Indeed "when physicians finally began to look seriously for mesothelioma [in the 1980's], they found it in abundance" (9).

At the end of the article, since no mesotheliomas were recorded in another analysis they conducted among the miners from the Asbestos Mountains, the authors tried to explain these results, introducing two concepts: latency and individual susceptibility, which were to become fundamental for the comprehension of the epidemiology of asbestos-related mesotheliomas. In particular, the authors stated: "it is possible that there has not been a sufficient lapse of time after exposure for tumour development in these cases. Further, the factor of individual susceptibility must also be considered" (25). At that time, they began to assume an additional theory that would be fully expressed by Wagner only some years later: "The South African finding has been confirmed that the association [of the mesothelioma] is with asbestos exposure, and not necessarily with asbestosis. In a number of cases the actual exposure has been slight, in one case three months of boiler lagging, and the latent period between initial exposure and diagnosis of tumour is again about 40 years" (22).

To complete the analysis of Wagner's 1960 studies, it should be noted that the literature reported by the authors did not (intentionally?) include prewar German articles and that Wagner, shortly after the publication of this famous article, left South Africa to continue his work in the UK. This move can be interpreted as a consequence of the acknowledgement the researcher deserved for his work, but it could be also looked upon as an unwanted exile, due to the reactions of South African asbestos industry (8).

The Italian contribution

Despite the non-conclusiveness of its results, Wagner's paper had a rapid diffusion and enjoyed great success both in the scientific community and in the media. Thus, it is interesting to recall the contribution to the enhancement of Wagner's results provided by the Italian occupational medicine community, especially Enrico Carlo Vigliani (1907-1992), then director of the "Clinica del Lavoro" in Milan (3).

Firstly, it should be noted that in Italy other specialists had dealt with mesothelioma before occupational physicians. The only Italian article quoted by Wagner in his 1960 paper was written by two internal medicine specialists belonging to Gino Patrassi's team in Padua, Bovo and Belloni, who supported the hypothesis of the primary origin of pleural tumours (2). In 1961, the surgeon Melis and the pathologist Agrifoglio from Genoa clarified all clinical and histological doubts on the existence of primary pleural mesothelioma. However, they did not quote Wagner's paper and overlooked the relationship between this form of cancer and

asbestos, that could be assumed considering the occupation of the twenty-four cases of mesothelioma they described (3, 12).

In the field of occupational medicine, the greatest Italian contribution to the study of asbestos-related mesothelioma was provided by Enrico Vigliani (3). When he became Editor-in-Chief of the journal "La Medicina del Lavoro", he contributed to the diffusion of the German studies on the carcinogenicity of asbestos, forerunners of Doll's studies (19). In the 1960's Vigliani's scientific authority was widely recognized internationally, as confirmed by his appointment as Secretary General of the ICOH (*International Commission on Occupational Health*) in 1957. Two years later, Vigliani was one of the participants of the *Pneumoconiosis Conference* in Johannesburg and on that occasion he was interviewed by a local paper, *The Sunday Times*, on the results of Wagner and Sleggs. The next day the journalist ran a story under the dramatic headline "Asbestos: the Killer Dust" and in this way, Vigliani's interview led to the first success of Wagner's studies in the media, endorsing their subsequent publications (11). Moreover, the success of the *Pneumoconiosis Conference* in Johannesburg provided impetus for what is considered as one of the most important conferences in the history of asbestos, chaired by Irving J. Selikoff (1915-1992) in October 1964. During this event, asbestos-related cancer cases from around the world were presented (10). The Italian contribution was presented by Vigliani, who examined the causes of death of 172 workers compensated for asbestosis by the *Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro* (the Italian Workers' Compensation Authority), between 1943 and 1964, in two Italian regions, Piedmont and Lombardy. Vigliani emphasized that fifteen patients suffered from lung cancer and three from pleural mesothelioma. In addition, another case of lung tumour and three cases of pleural tumours were diagnosed amongst workers who were still alive. The comparison of these data with necropsies performed on 24,700 subjects over 40 years of age in Turin, Milan and Pavia confirmed that workers compensated for asbestosis had a higher mortality for lung cancer and pleural mesothelioma (20).

Conclusions

As previously mentioned, immediately after its publication in 1960, Wagner's paper radically changed the scientific knowledge of asbestos-related cancer and produced a great impact on the economy and the legislation of most Western countries, up to the banning of any type of asbestos some decades later. From a scientific point of view, the paper contained "much of what we still know about malignant mesothelioma" (14). In spite of its enormous impact on occupational medicine, it is curious to observe that it was not written by specialists in this field. Moreover, it recognized occupational exposure only in a few cases (8 out of 33 cases, less than 25%) and almost all the observations were drawn from exposure outside the workplace. For this reason, the paper can be looked upon as one of the first studies that recognized a dual (occupational and environmental) aetiology for a disease (in this case, a cancer). It went beyond the traditional investigation of a sole occupational cause, introducing the new concept of "occupational and environmental disease". Re-reading Wagner's paper enables us to understand its modern approach, especially when the authors identify three fundamental principles of the epidemiology of occupational tumours and particularly of asbestos-related mesotheliomas: the need to identify the exposure to a carcinogen even at low doses and in the absence of asbestosis; the long latency period of mesothelioma; the influence of individual susceptibility.

Afterwards, together with John Gilson (director of the PRU) and Walter J. Smither (chairman of the Asbestosis Research Council), Wagner published a letter in the BMJ soliciting their colleagues to send "information concerning any patient in whom this type of tumour has been diagnosed" (18). In the UK this letter led to the establishment of the "Mesothelioma Register" which supplied much data on this tumour in the following years (1).

In the field of pathology, Wagner's work led to supporting the hypothesis of the primary origin of pleural tumours, thanks to the collection of biopsy and necropsy cases with a detailed description of

the techniques utilized and of the specimens analyzed.

In the following years, some epidemiological data supported the hypothesis that chrysotile was much less hazardous than crocidolite, and its role in the genesis of mesothelioma was minor. Wagner strongly opposed this theory and in 1979, as a panel member of the *International Agency for Research on Cancer* (IARC), he endorsed the finding that chrysotile, too, causes mesothelioma, leading the IARC to recognize the carcinogenicity of any kind of asbestos. As the evidence linking chrysotile to mesothelioma continued to accumulate, Wagner paradoxically changed his mind, claiming the "innocence of chrysotile to humans". In particular, in one of his last letters Wagner summarized in the following terms his updated and "conclusive" thoughts on the relationship between asbestos and mesothelioma: "The vast majority of mesotheliomas are associated with exposure to crocidolite asbestos. A small number of cases have been recorded following exposure to other forms of amphibole asbestos: amosite, tremolite, and anthophyllite. No mesotheliomas have been shown to have occurred in chrysotile exposed workers, unless the exposure has been intense and for more than 20 years. In addition, there must be tremolite contamination of the chrysotile. Two other facts are of great importance: 1. The majority of these tumors occurred following prolonged exposure to large quantities of fiber. This situation rarely exists today. 2. There is a "natural" incidence of these diffuse mesotheliomas. At least 10% of these diffuse mesotheliomas occur without [occupational or environmental] exposure to asbestos dust, and sporadic cases of these tumors were reported before the widespread use of asbestos" (24). These latest statements were looked upon as a "volte-face" and put Wagner at odds with the leading researchers in the field who started to harshly criticize him (9). Actually, it is worth considering the last sentence of Wagner's letter, remembering that even in the 1960 paper no relationship between mesothelioma and occupational and environmental asbestos exposure was found in one case out of thirty-three. Even today, analyzing data from all the Mesothelioma Registers, there is a percentage of cases where asbestos exposure is defined as "possible" or "unknown". This percentage could also include the "natural incidence" (10%) postulated by the South African pathologist in his last letter.

Via this historical analysis we have been able to describe the contribution to the study of the relationship between mesothelioma and asbestos provided by the Italian scientific community in the 1960's, particularly by Enrico Vigliani. The participation of Italian scientists in the mesothelioma debate in those years is often neglected by international historians and should be re-appraised.

In conclusion, the paper written by Wagner, Sleggs and Marchard in 1960 can be considered a milestone in the history of occupational and environmental medicine, but also in the history of pathology, oncology and epidemiology. As mentioned, the contents of the 1960 paper are still extremely modern and Chris Wagner's change of mind at the end of his life should not influence the general opinion regarding this article, whose value is irrefutable. Therefore, it should be carefully reread, especially by young specialists in occupational medicine and students, if they wish to understand not only the subsequent evolution of knowledge on the relationship between asbestos exposure and mesothelioma, but also the development of occupational medicine with particular reference to the relationship of environment with cancer.

NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED

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