Chapter

Cosmetic Talcum Powder as a Causative Factor in the Development of Diseases of the Pleura

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Abstract

This chapter describes some of what is known about the effects of talc as cosmetic or pharmaceutical talcum powder on the pleura and other organs of the human body. It further describes some of the already known mechanisms of how it interacts with human cells and tissue to cause diseases, specifically in the pleura. The effects of talcum powder are well established that the range of diseases include clinical or subclinical inflammation, granulomatous disease and tumors, in the pleura mainly mesotheliomas. Also included are some preliminary evidence indicating what happens in vitro with macrophages in response to talc morphologically and the consequences following the treatment with the release of factors such as chemokines, cytokines and oxidants.

Keywords: cosmetic talcum powder, pleura, granulomas, mesothelioma, lung cancer, asbestos

1. Introduction

It has been demonstrated that both asbestos and talc can and does cause diseases of the pleura [1–9]. Asbestos has been shown to cause the development of benign lesions in pleura termed pleura plaques [10]. These plaques have become a hallmark for asbestos exposure [10–12]. These lesions correlated with interstitial fibrosis of the lung parenchyma [2] and the development of lung tumors [13]. These lesions allow for attribution of asbestos as a causative factor in the development of lung tumors in the absence of interstitial fibrosis [12]. Pleural plaques is also a lesion that indicates asbestos exposure in the absence of interstitial fibrosis and/or lung tumors [12]. Asbestos has been shown to be the cause of tumors of the pleural lining, mesotheliomas [2]. It has been shown that mesotheliomas in men were mostly seen in those men with occupational histories of exposure to asbestos [14]. Similarly, it was demonstrated that the wives of these men that were exposed and women that worked with asbestos also developed the pleural plaques, interstitial fibrosis and mesotheliomas [4, 8, 15, 16]. It was understandable how the asbestos caused the lesions in the pleura of women working with the asbestos, however, it was not initially understood how the wives or children of workers developed these lesions until investigators looked at the clothing of the husbands and determined that they were

bringing the asbestos home and the wives or children were exposed cleaning their clothes [15, 16]. However, only about 30% of all the mesotheliomas found in women could be attributed to exposure to asbestos [17]. The remainder of women with mesotheliomas were considered idiopathic because they could not be attributed to a specific asbestos exposure.

With that in mind, I will turn to talc as a cause of pleural diseases. It has been shown that talc causes pneumoconiosis [1]. In some people exposed to talc via inhalation, they have been shown to develop granulomatous lesions in the lung [1]. It was determined that these lesions were developed from a macrophage response directly due to the talc by finding the talc with the macrophages and giant cells in the lesions [18]. Based on the knowledge that the talc will cause a granulomatous reaction with fibrosis, pharmaceutical talc was being used in patients with pleural mesotheliomas who developed pleural effusions. The patients almost always developed pleural effusions with pleural mesotheliomas which had to be drained frequently. It was then determined and that by injecting the pharmaceutical talc into the pleural space, it would insight a granulomatous response which would fill the space between the visceral and parietal pleura with a granulomatous response followed by fibrosis alleviating the need to drain this fluid [19]. This occurred in 100% of the individuals that the talc was injected, as compared with a very low percentage of people getting talc granulomas from breathing talc [19].

It is the purpose of this chapter to further describe the effects of talc, particularly cosmetic talcum powders in the causation of diseases of the pleura. This includes the development of pleura plaques, granulomas and mesotheliomas.

2. Background

It is important to understand how foreign materials such as cosmetic talcum powder can get to the pleura to cause diseases. For the particles contained in the cosmetic talcum powder to get to the pleura under normal circumstances after inhalation would be that these particles are phagocytized by macrophages of the lung and these macrophages enter the lymphatic system and are carried in two directions based on the drainage of the lymphatic system of the lung [20]. The macrophages are carried to the regional lymph nodes along the respiratory bronchial tree and up along the trachea. Alternatively, the lymph drains to the pleura. Another route, although not as good in distributing to the pleura is if the macrophages should enter the blood stream, mainly into the capillaries of the alveolar septa, at the peripheral gas exchange surfaces of the lung [20]. Under those situations, the talc can be taken anywhere in the body. The last way is that it is injected directly into the pleura, termed pleurodesis [21].

Once in the lung, lymph nodes or pleura, the particles induce reactions within cells which result in the production of cytokines, chemokines and oxidants, all of which are responsible for the inducing an inflammatory response and the mechanistic steps in the process of compensated healing or fibrosis [21]. The size of the talc particles appear to be critical to the type of response the cells and the tissue mount [22]. The particle size of cosmetic talc is significantly smaller than that used for talc pleurodesis and therefore the response is very different [22]. The inhalation or injection of this smaller cosmetic talc has a much greater detrimental effect by the inflammatory response it elicits [22].

Similarly, these same cells produce oxidants following activation by the presence of the components of the cosmetic talc powder in addition to producing cytokines, chemokines, IL-6 & 8; TGF-beta, which attract inflammatory cells as well as cells that produce fibrosis [23]. Oxidants are extremely reactive and have the ability to

do significant damage to resident cells to cause injury to cells, stress the cells, and cause DNA damage [24]. Such DNA damage can and will cause mutations which can result in cancer development [24]. However, the release of chemokines which stimulate and attract other inflammatory cells, neutrophils, which further release similar factors as the macrophages and but most importantly, additional oxidants. Such mechanisms of injury has been shown over and over again to correlate with the development of cancer, specifically, the resident cells and therefore mesotheliomas [25]. These mesotheliomas in response to the talc has been attributed to contaminating asbestos [25–27]. However, in all the studies, whether looking at mortalities and percentage of mesotheliomas based on exposure to talc or epidemiological studies, there have been none in the past that actually put together all the components of age, sex, amount of exposure and documentation of tissue digestions of lungs, respiratory lymph nodes or abdominal organs, including ovaries to attribute the finding of talc and/or asbestos together. Therefore, it is difficult to conclude that asbestos was the only contributing factor. The talc may well be a contributing factor in both the development of the pleural plaques, mesotheliomas and abdominal mesotheliomas and ovarian cancers.

3. Common cases

The author has now had the opportunity to evaluate approximately 100 plus cases of mesothelioma, pleural and abdominal, of both men and women with only a history of exposure to cosmetic talcum powder, some with exposure to a single cosmetic powder and others to multiple types. However, none of these patients have indicated, based on extensive histories, that there was exposure to occupational or para-occupational to a commercial asbestos or products containing added asbestos. There are a few cases where there may have been brief, single exposures to possible sources of products that may have contained asbestos. It is important to emphasize "brief" as compared to everyday if not multiple times per day exposure to cosmetic talcum powder. The logic only reflects that the cosmetic talcum powder would represent the overall, great majority of particles and fibers found in the lungs and lymph nodes in these patients and would dictate the source of these structures would be from the cosmetic talc rather than the brief potential exposure to another questionable unproven source. The findings of digestions of the lungs and the lymph nodes of the patients show basically all the same structures. Some of the cases are reported as a case study, which is currently under review. One study where that has been published describes the case and what was found in the digested tissue as well as the testing of the cosmetic talc and to correlate it with the potential to breathe both the asbestos fibers and the talc [28]. All of the patients have talc particles, aluminum silicates, some with magnesium, some with iron and some with both. There can also be silica crystals and fibers, silica, talc and aluminum silicates. Further, most of the patients also have asbestos fibers, primarily anthophyllite and tremolite. Even though it has been shown that many of the cosmetic talcum powder containers sold by at least one company also contained chrysotile type asbestos the chrysotile was never found. Based on the ability of the human cells to break the chrysotile down and dissolve it and or move it out of the initial sites, it would not be found in digestions done many years after exposure. The presence of either type of asbestos or both are reflective of the types and time frame of the cosmetic talcum powder used. The source of the talcum powder, meaning the mine source and location of the talc may result in the presence of the particles and fibers that contaminate the cosmetic talcum powders as it solidified millions of years before. It is not uncommon that over many years of use and exposure that it is possible for

such exposures to be from multiple sources, mines. Therefore, it is not uncommon to find all of the particles and fibers present in most of these patients.

It is important to address the issue of what has been termed intergrowths. Some asbestos analysis laboratories do not confirm or report fibers that can be termed intergrowths. These intergrowths are attributed mostly to anthophyllite fibers. The most common source of such intergrowths has frequently been stated in courts across our country by lawyers and their expert witnesses that suggest the only source of these intergrowths occur where anthophyllite veins meet with talc deposits. This can be true, but more commonly talc is an integral component of anthophyllite all the time [29]. If a mineralogist looks at anthophyllite fibers by what has been termed zone-axis analyses where the anthophyllite is analyzed by tilting and rotating to find possible co-mingling of some talc with the anthophyllite and therefore making the false claim that it is an intergrowth making the fiber non-asbestos. This is also true for transitional fibers because portions of the fibers are anthophyllite. If that portion of the fiber is broken off there would be no way to distinguish it from any other frank anthophyllite fiber. However, it could be interpreted that the combination of primarily an anthophyllite fiber with the talc between the fibrils may be the perfect carcinogen based on action of both types of crystalline structures being present. It is also based on their abilities to cause inflammation by release of chemokines, the development of fibrosis by the release of cytokines and the development of cancer by direct mutation or the production of oxidants which can cause injury or mutation. Therefore, in spite of the fact that most every asbestos analysis laboratory uses selected area electron diffraction (SAED) as the gold standard for defining asbestos type and distinguishing it from a nonasbestos fibers, in this particular case, spending hours manipulating a fiber to show it may have a talc component is a ridiculous exercise knowing that the primary features of this structure represent an anthophyllite fiber and even if it has a small talc component, from a biologic standpoint the cell will see it as an anthophyllite asbestos fiber. This entire concept of an intergrowth is just detraction of reality by a laboratory trying to, in most cases, satisfy a defendant company trying to misrepresent other laboratory findings. However, from a mineralogic standpoint they are fine attributing such a fiber to that of an intergrowth, but it should never be excluded from being called an anthophyllite asbestos fiber. Therefore, the combination of morphology, EDS and flat plane SAED is sufficient to identify an anthophyllite fiber for the purposes of asbestos analysis in human tissues.

There have been many studies linking the use of cosmetic talc and the development of both mesotheliomas, plural and abdominal and ovarian cancer [10, 13, 30, 31]. Most of these studies are based on the patients' reporting significant exposure to cosmetic talcum powder and no exposure to any other asbestos containing product. This leads us to two additional issues that have yet to be resolved: (1) Was the cosmetic talcum powder adequately contaminated with asbestos for the asbestos to be the causative factor all on its own or does the talc itself contribute to the process of tumor development? (2) In the past, there has been an extremely high rate of mesotheliomas in women, as much as 70%, that have been termed idiopathic. Clearly these women when questioned about their medical histories have indicated no evidence or history of asbestos exposure. However, it has become clear that in the past most physicians were not considering cosmetic talcum powder an asbestos product nor were they considering it a source of asbestos that would account for the development of a mesothelioma. Yet again, that appears to exclude the talc itself or its other contaminating components such as fibrous and platy aluminum silicates and fibrous and crystalline silica particles.

To support this concept that other components in the talcum powder may be carcinogenic, are reports attributing fibrous aluminum silicates to the development of mesotheliomas in the form of algorskite (palygorskite) [32]. We already know

and understand how talc, silica and aluminum silicates can cause the development of granulomas in the lungs and GI tracts of humans. This again is an inflammatory/immunologic mechanism predominantly in patients that are genetically predisposed. However, predisposed or not if these particles are in a large enough concentration it will produce these inflammatory responses in 100% of the patients. This type of reaction is now well documented as a contributing factor to the development of cancer as a promoter, but possibly as a carcinogen or co-carcinogen as well.

4. Preliminary evidence

With the above in mind, this author has looked directly at the interaction of the particles present in cosmetic talcum powder taken from a container previous extensively tested for the presence of asbestos, tremolite; anthophyllite; and chrysotile, and which no asbestos was found. The experiment was designed to put the cosmetic talc at a very low concentration 0.001 grams per ml distilled water into primary macrophage control cultures differentiated from human blood monocytes. The macrophages were cultured with the cosmetic talcum powder for 12, 24 hours and 3 days. At that point the cultures were fixed with glutaraldehyde and duplicate dishes were processed for observation by scanning electron microscopy (SEM) on the cover slips and the other dish was rubber policed to yield a cell pellet so it could be routinely processed for embedding in epon, ultrathin sectioned double stained and observed by transmission electron microscopy (TEM). The SEM allowed me to determine how the macrophages were collecting and engulfing the particles. The TEM made it possible to see in what structures the particles were contained and how the particles were interacting with the macrophage organelles and how they differ from normal differentiated macrophages.

The results of this preliminary study show that the macrophages engulf/phagocytize the particles (**Figure 1**). In many instances, the particles are just too large for the cells to completely engulf and they extend out of the cell (**Figure 2**). If these

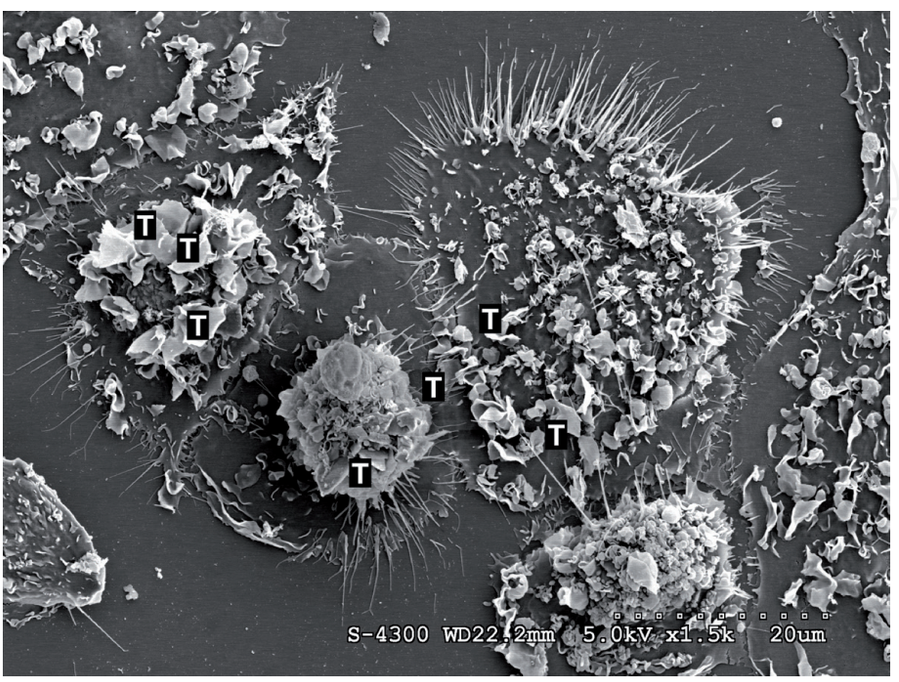

Figure 1.
Scanning electron micrograph (SEM) of a cultured human monocytes differentiated in macrophages collecting and engulfing the talc particles ***(T)****.*

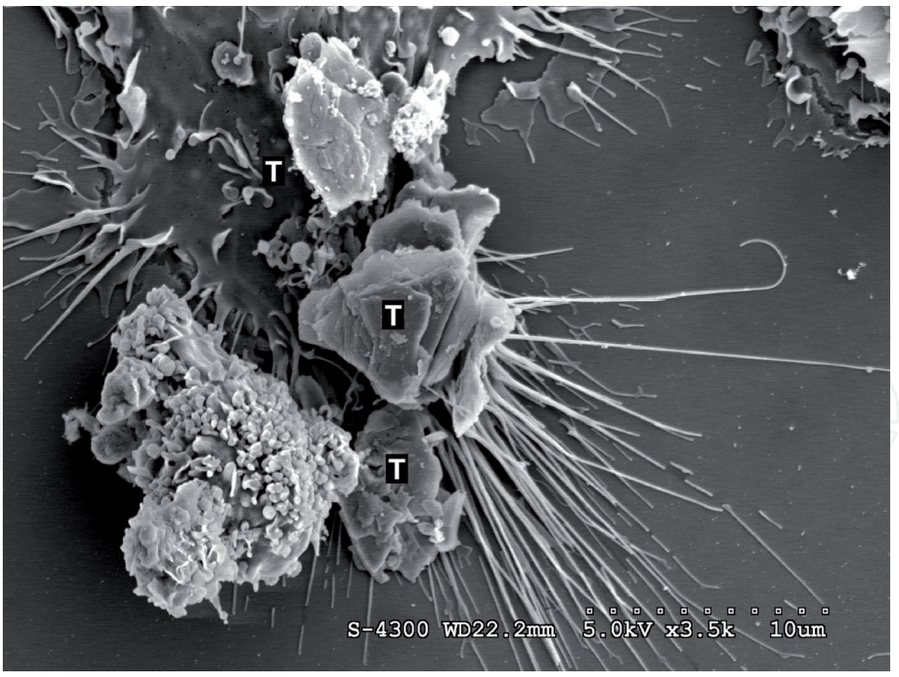

Figure 2.
*This SEM shows a cell after 3 days with talc **(T)** and the particle cannot be completely engulfed in the cell. During this process it is possible to see how intracellular molecules such as the chemokines, cytokines and oxidants can easily leak around the particles outside the cell.*

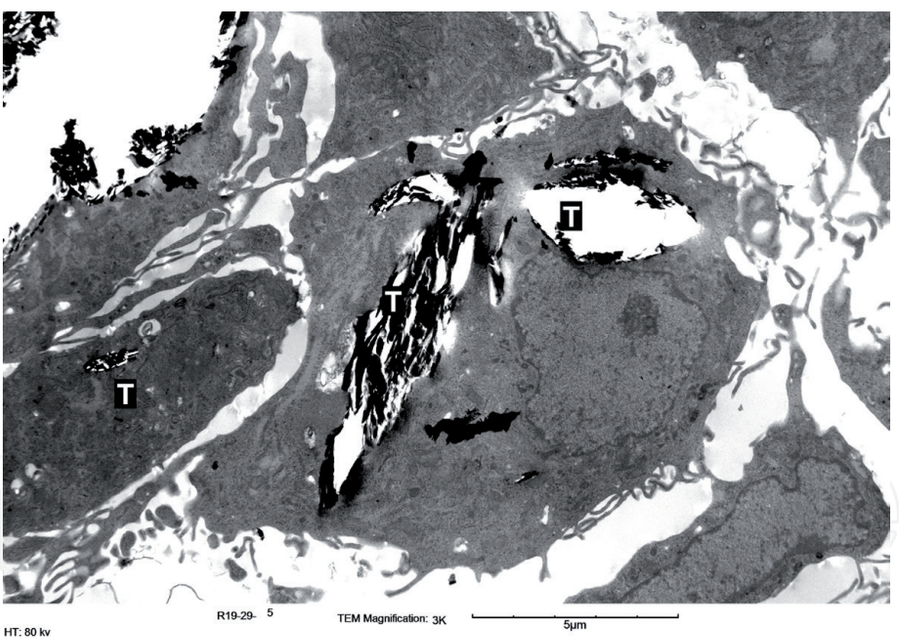

Figure 3.
*In this transmission electron micrograph (TEM), it is possible to see the talc particle within the cell. However, because the section of the cell is so thin, it is not possible to determine if the particle has been completely engulfed or not. However, based on what was visualized by SEM, it is likely that the larger talc **(T)** particles are not completely engulfed.*

cells are observed in thin sections by transmission electron microscopy (TEM) it is difficult to determine if the particles are completely within the cells or partially in and partially outside (**Figure 3**). This is similar to what is seen with asbestos fibers that are longer than 10 micrometers. This is very much like inflammatory cell attempting to phagocytize deposits in the kidney glomeruli and just cannot because the deposits are in the basement membrane. This is termed frustrated phagacytosis and results in the leakage of lysosomal enzymes and many other chemokines,

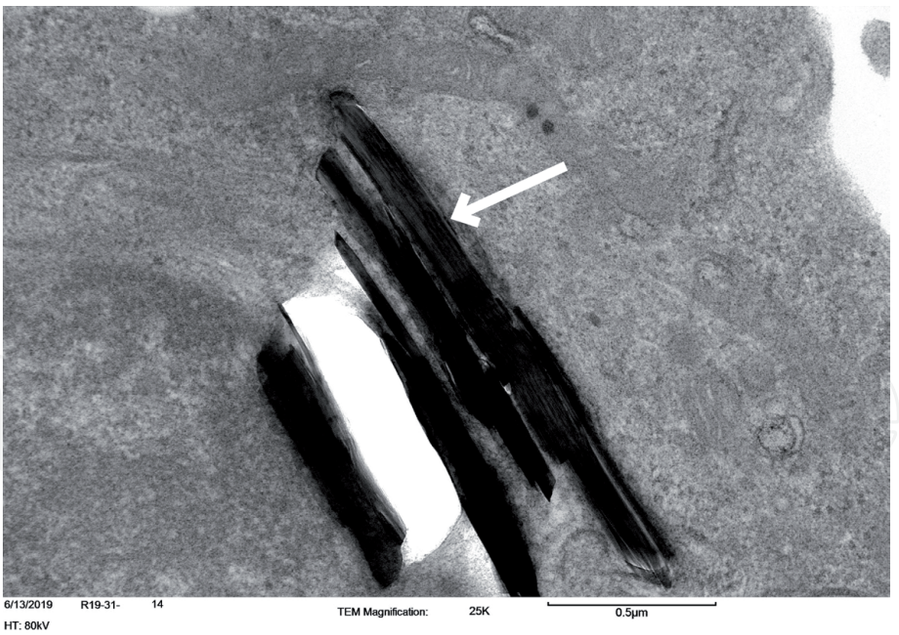

Figure 4.
Normally anything that is endocytosed by macrophages or phagocytic cells are surrounded by the plasma membrane as it endocytoses something. What is very interesting with the talc is that there is no complete membrane surrounding the particle. The membrane is discontinuous within the cell (arrow).

cytokines and oxidants from the macrophages. TEM analysis of the cells exhibited particles in the cytoplasm of the cells and they were not completely enclosed by a single membrane in the 12, 24 or 72 hours specimen (**Figure 4**). The most interesting finding is that these particles as they break down within the cell cytoplasms due to enzyme activity or not do not exhibit being membrane bound (**Figures 5A**, **B**). Remnants of membrane, presumably plasma membranes, can be seen but the talc particles are found mostly free in the cytoplasm of these cells (**Figures 5A**, **B**). It was possible to see smaller particles completely engulfed into the cell that were free, not membrane bound (**Figure 6**). These particles can be seen very close to the nucleus of the cell making direct mechanical interaction with or without cell division possible (**Figure 7**). The significance of this has very detrimental implications for alterations of cellular function. If and when these particles enter mesothelial cells or even lung cells and are free to interact with surrounding organelles and other cellular components, the cells may be stimulated to divide and in doing so during division the chromosomes and DNA are exposed to these particles which can alter the DNA and chromosomes mechanically by charge distribution or any other mechanism including direct oxidant injury to the DNA. This can lead to mutations that will lead or result in the development of tumors.

Support for the morphologic criteria is the biochemical and immunologic criteria showing that cytokines, chemokines and oxidants are released in response to the frustrated phagocytosis. **Figures 8** and **9** support the cytokine up regulation. These are similar, if not exactly the same criteria that had been reported for the interaction of asbestos fibers and macrophages over the years. Based on these preliminary in vitro results, it is not a far reach to implicate talc and its contaminating silica and aluminum silicates as a causative agent in the development of mesotheliomas, lung tumors, gastrointestinal tumors, and ovarian tumors.

Further, the proof of these basic facts and the epidemiologic study of cases that this author has done of asbestos fiber and particle analyses on over 200 cases of men and women who have only exposure to talcum powder with no exposure to any other source of asbestos, and have developed mesotheliomas, pleural and abdominal, and ovarian cancer of epithelial origin. It should be noted here that the

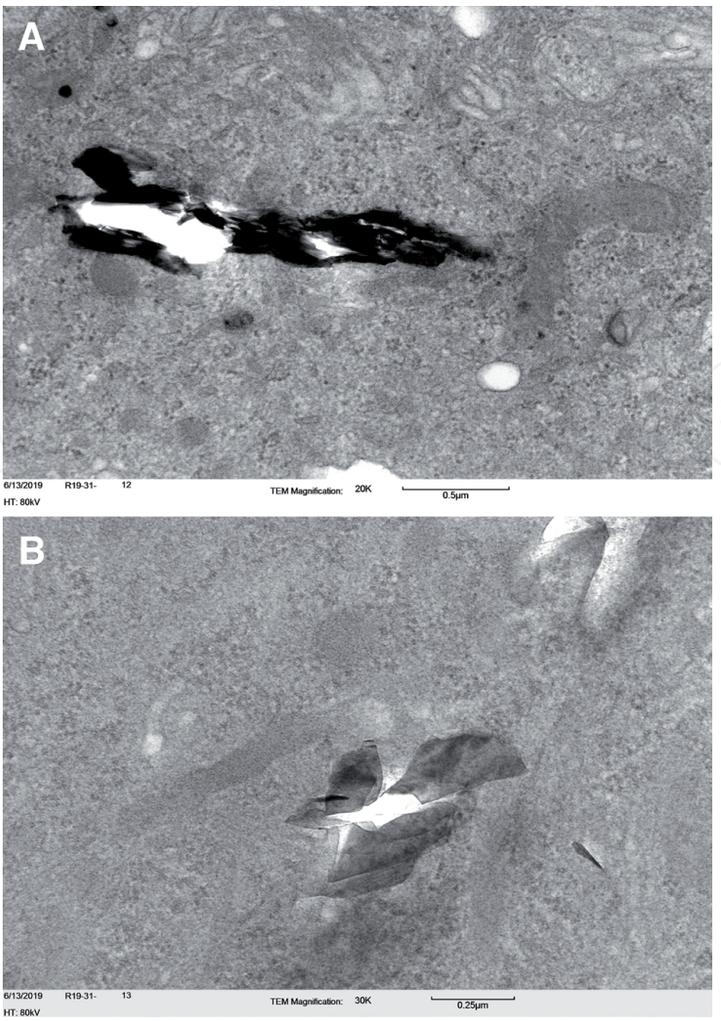

Figure 5.
(A and B) When one observes even the smaller particles that are presumed to be completely within the cell, it is not possible to identify a complete membrane surrounding the particles. It appears that the particles unlike other components taken up by cells, these apparently can be found naked in the cytoplasm.

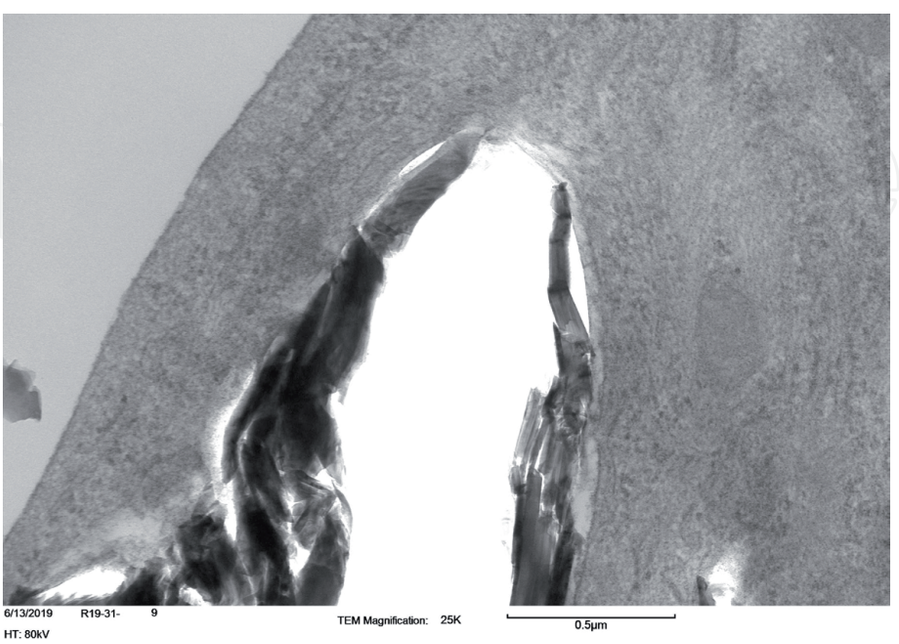

Figure 6.
The larger particles clearly exhibit an absence of membrane and it presence in the cytoplasm where lysosomes and other molecules within the cell can directly interact with the talc particles causing injury to the and leaking components into the media in this case or in tissue to adjacent cells.

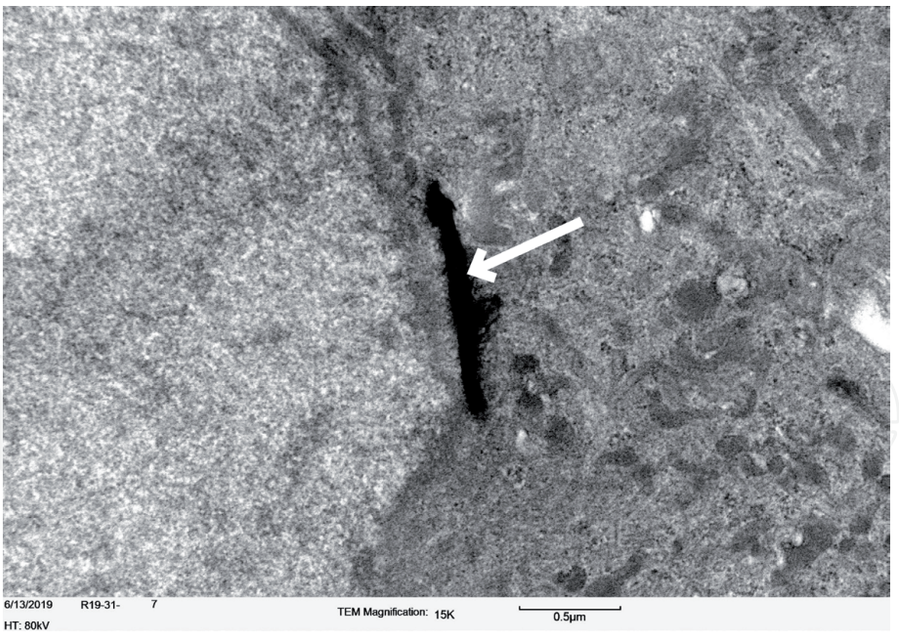

Figure 7.
These small particles and possibly even the larger particles make their way right to the nucleus (arrow).

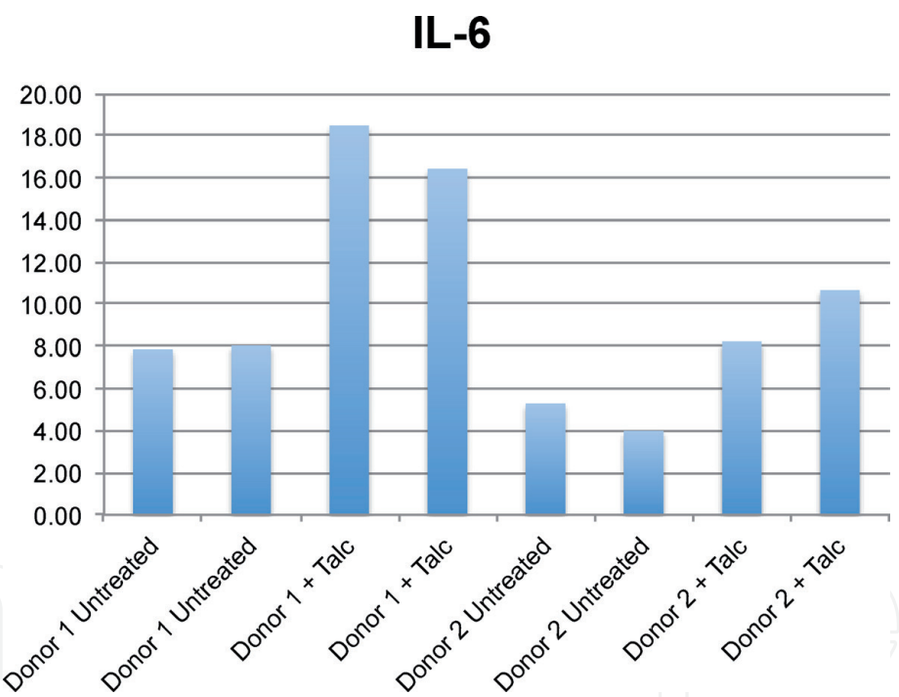

Figure 8.
This is a bar graph exhibiting the results of the IL-6 measurements from the 2 patients under the 3 conditions of control, cultures without talc and with talc added.

outer lining of the ovaries that give rise to the tumors are basically mesothelial cells, just on the surface of ovaries. The correlation of finding significant amounts of talc, aluminum silicates, crystalline silica and in more than half the cases asbestos fibers as compared to background controls with none of the fibers and particles discussed above, supports the concept that cosmetic talcum powder is the causative factor in the development of the mesotheliomas and ovarian cancer. This applies to both abdominal, pleural and ovarian cancer, however, the abdominal mesotheliomas and ovarian cancer represent a cleaner model since analyses of lung and pulmonary lymph nodes frequently contain some talc, aluminum silicates and crystalline silica from the environment and nonasbestos containing materials. However, these

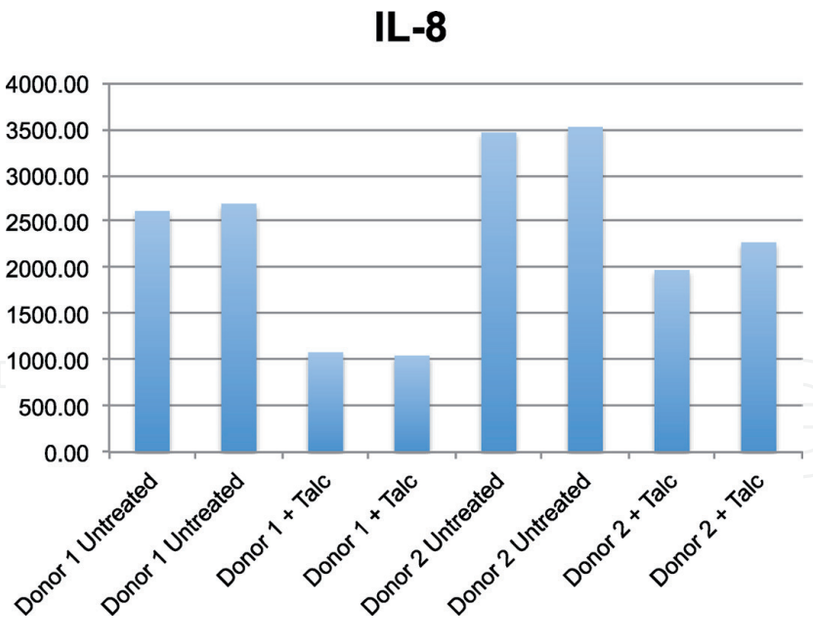

Figure 9.
This is a bar graph exhibiting the results of the IL-8 measurements from the 2 patients under the 3 conditions of control, cultures without talc and with talc added.

components are in relatively small quantities as compared to those individuals that have used cosmetic talcum powder on a regular basis.

5. Summary

There is now significant growing evidence based on basic scientific studies and epidemiologic studies of those patients exposed to cosmetic talcum powders on a regular basis with correlation of isolation of talcum powder components in significantly greater concentration than the contaminating asbestos, that the talc or other aluminum silicate components found in high concentration in the talcum powders strongly implicate the talc itself as a causative factor in the development of all the same lesions: granulomas, fibrosis and tumors, as seen with asbestos. Due to the relatively small amount or absence of an iron oxidant component in the talc and aluminum silicates, it is likely that without a tremendous load the detrimental effects may take years to develop in patients that are predisposed genetically to the actions of these talc particles. This phenomenon may be very much correlated to the development of similar lesions by chrysotile asbestos, having a longer latency from that of commercial amphiboles amosite and crocidolite.

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