

OBSERVATIONS CONCERNING ALVEOLAR DUST CLEARANCE *

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INTRODUCTION

Before beginning my observations on alveolar dust clearance, some of the problems inherent in studies of this subject should be mentioned. In their excellent book, *Pulmonary Deposition and Retention of Inhaled Aerosols*, Hatch and Gross¹ state, "Owing to the wide difference in experimental results reported by the various investigators, it is not possible to draw firm conclusions with respect to pulmonary clearance characteristics." In 1970 Kilburn commented further in his paper "Alveolar Microenvironment":² "Because no one has even seen or placed a tracer into a living alveolus this paper must be deductive, hypothetical, and speculative." After this conciliatory introduction, let me mention a further weak point. In reviewing basic attributes of alveolar clearance, one has to rely on data which very often lead only indirectly to the description of the processes under discussion. One example is the technique used in the quantitative determination of lung clearance. The amount of particles cleared in a certain period of time after exposure is estimated indirectly, by subtracting the amount retained in the lung after a given period from the amount deposited during exposure.

Although a number of questions remain to be answered, the mechanism of particle clearance from the respiratory system has been broken down into at least two basic components. The first, called rapid or early, is connected mostly with clearance of particles deposited from the inhaled air at the respiratory airways. The second, called slow or long-term, is associated with all the remaining possibilities, e.g., alveolar and lymphatic clearance. The terms used to describe the components are related to clearance velocity and time, the anatomy of the lung, or the mechanisms involved. The Task Group on Lung Dynamics³ proposed a dust clearance model that enumerated ten different absorption and translocation processes associated with the clearance of three lung compartments. The model defines two clearance phases from the pulmonary region—the compartment consisting of the respiratory bronchioles and all the structures connected with the alveoli—phases that depend on macrophages coupled to the ciliary-mucous transport process. It is to this part of the lung clearance process that the present paper is addressed.

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QUALITATIVE CHARACTERISTICS OF DUST CLEARANCE

Evidence of the onset of alveolar clearance in rats was studied, using light microscopy. The animals had been exposed to TiO_2 particles in a dusting chamber. Five minutes after beginning the exposure few particles were seen in the alveoli, so that one could not make a good judgment about their disposal. Following a 30-minute inhalation, the particles were numerous; they were located not only on the alveolar walls, but also intracellularly. Some of the alveolar macrophages laden with particles had at that time already been carried on the "ciliary escalator." Two days after commencing the seven-hour exposure, the number of alveolar macrophages was substantially enlarged, and most particles were located intracellularly. The shape of most of the macrophages was rounded, which may have been an artifact: cells passing at the moment of fixation through narrow structures and thus trapped in that position retain the shape of a moving macrophage. At this point a few particles could already be located in the interstitial space.

From these findings, let me point out the following:

1. The onset of alveolar clearance begins immediately, overlapping in time with the rapid clearance of particles from the tracheobronchial system.

2. The number of macrophages increases rapidly over several hours to a peak and slowly decreases. Also reported by LaBelle and Brieger⁴ and Sanders.⁵

3. The motility of the macrophages is sustained in the environment of the alveolus, even with a great number of phagocytized TiO_2 particles.

4. After the initiation of alveolar clearance by macrophages, the consecutive removal of phagocytes with particles from the alveoli is slower than the replacement of cells, so that buildup occurs. (Also reported by Gross *et al.*⁶)

5. There is no direct evidence for answering such questions as: How are the macrophages and/or particles translocated to the ciliary region? How are particles transported through the alveolar wall into the interstitial space?

6. When discussing solubilization of particles within the lung—a significant factor in many of the ten translocation processes mentioned by the Task Group on Lung Dynamics³—the localization of the particles at or in different lung structures should be considered.

RETENTION HALF-TIMES

A quantitative approach to the measurement of retention will obviously yield more information than the qualitative approach, including an estimate of the retention half-time. Through analysis of the lungs of serially sacrificed animals, we found the retention half-time in our experiments with a single TiO_2 exposure to be 14 days, for the first eight days, and 88 days thereafter (FIGURE 1). An uncertainty was created by using the eight-day point in the first clearance phase. This may have shifted the estimate of the retention half-time in the first eight days to higher values.

I believe that the cleared particles were removed primarily by the mechanism which depends on alveolar macrophages. Indirect evidence for this conclusion is the unmeasurable translocation of TiO_2 into other organs (except of the gastrointestinal tract of the animals) at the time when lung clearance was surveyed. The half-time value of 88 days nearly coincides with the 90-day

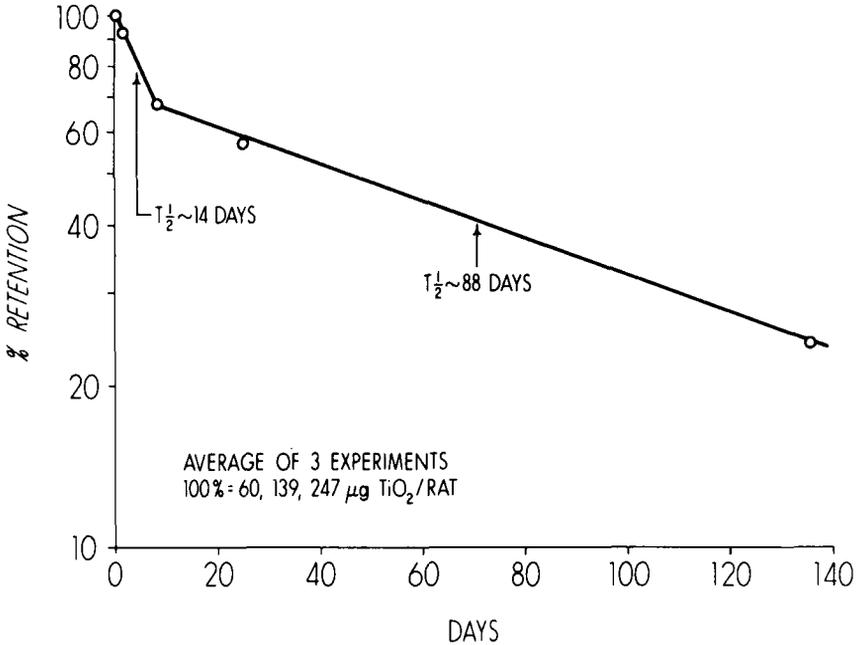


FIGURE 1. Retention of TiO_2 particles in the lung after one exposure.

constant of the above mentioned model for this class of inorganic compounds.³ This group also includes silica. The comparable half-time for silica may be 60–80 days.^{7, 8} LeBouffant⁹ found that the clearance of the fibrogenic quartz dust and the nontoxic TiO_2 dust were very similar in the eight weeks following exposure. In the first two months after a single exposure, then, it appears that the removal of dust is influenced by the physiochemical properties of the particles (solubility, size), rather than by their fibrogenicity.

INFLUENCE OF LUNG BURDEN ON DUST CLEARANCE

By changing either the concentration of the particles in the dusting chamber or the exposure time, one may influence the initial lung burden of the experimental animals in a predictable manner.²⁴ Expressing the dust retained at different times after exposure as percents of the initial lung burden, one arrives at, within a certain range, amazingly similar numbers. Three experiments are shown (FIGURE 1) with initial lung burdens of 60, 139, and 247 μg per rat, respectively. In all three experiments after 88 days (half time), 50% of the initial lung burden was cleared. Hence, comparable rats were able to eliminate from the alveoli in the same time 20, 70, and 120 μg of TiO_2 , respectively. The upper limit of the range where such an effect may be expected is certainly higher than 247 μg per rat. LeBouffant⁹ has seen this effect in rats with an initial lung burden of about 200–800 μg of TiO_2 . In Klosterkötter's and Bünemann's⁸ experiments with quartz dust, the clearance half-time started to

increase at a lung burden around one mg per rat. Hence, lung clearance has a reserve capacity of at least one order of magnitude. Until now, it was not possible to mobilize this capacity by artificial or experimental means.

INFLUENCE OF SINGLE OR MULTIPLE EXPOSURES

The experiments mentioned have been performed under simplified conditions, one of which is the use of a single exposure. In another study, I have shown¹⁰ that a repetition of exposures (2-4 \times) impairs the clearance of TiO₂ particles in the first eight days after the last exposure. This finding is in agreement with results of Morrow and colleagues¹¹ and Downs and colleagues,¹² who found longer clearance half-times when performing multiple uranium dioxide exposures in dogs. Comparing the results of LeBouffant's experiments⁹ using a single exposure of TiO₂ with the multiple exposure experiments of Policard and colleagues¹³ performed at the same laboratories, one may similarly see a clearance impairment after repeated exposures. Stretching the interval between four exposures from one to 25 days, we could eventually find clearance comparable to that found after a single exposure (TABLE 1). The picture may change again if hundreds of exposures are used. Stöber and colleagues¹⁴ reported that in rats exposed to quartz as well as in coal miners with no pathological changes in the lung, alveolar clearance of particles increases with increasing alveolar retention. In other words, during chronic exposures there is no linear relation between retention of dust and time. The retained amount of dust per unit time is smaller with increasing exposures. According to Einbrodt,¹⁵ the retention of dust in coal miners' lungs was greatest in the first ten years of exposure. After 30-40 years of employment only one-third of the amount found after the first ten years of exposure is added to the retained dust. The mechanism of this decreasing retention is not understood; Weller¹⁶ came to opposite findings even when using a coal-quartz mixture in experiments on rats. However, his animals had some silicotic changes compared with the animals of Stöber and colleagues.¹⁵

TABLE I
THE INFLUENCE OF THE LENGTH OF INTERVALS BETWEEN EXPOSURES
ON LUNG CLEARANCE OF TiO₂ PARTICLES

Rat	No.	Exposure mg/m ³	hrs	Interval days	Initial Lung Burden μg/rat	Retention (%) After Exposure at Day	
						8	25
1	4	~ 15	7	1	355	92	64
2				2-3	427	97	57
3				10	342	86	59
4				25	440	71	58
5	1	~ 15	7	—	125	66	58
6	1	~ 50	7	—	350	77	58

CHANGE IN CLEARANCE EFFICIENCY

It is generally believed that the overwhelming accumulation of dust in the lungs which eventually leads to pathologies must be blamed, at least partially, on failure of the clearance mechanism. This view may find support in the paper of Rossitter and colleagues.¹⁷ These authors report that the pneumoconiotic changes in the lungs of coal miners increase as the amount of dust in the lungs increases, from category 0 with 4.2 g of dust per lung to category III with 19.1 g of dust per lung.

In these terms, pulmonary clearance very effectively decreases the accumulation of the inhaled dust particles. According to different calculations,^{1, 18} 60–97% of the particles supposedly deposited in the alveoli during a lifetime exposure are eliminated from the lungs.

Let me mention at this point some data showing a change in alveolar clearance capacity when particles are introduced experimentally. LaBelle and Brieger¹⁹ stimulated the elimination of a small amount of uranium (5 μg) by use of additional inert coal. Elimination of SiO_2 particles was accelerated by polyvinylpyridine-N-oxide (Schlipkötter).²⁰ In our experiments²¹ the clearance of SiO_2 particles was enhanced by Trypan Blue injection or by preexposing the animals to a short exposure of TiO_2 . Fisher²² increased particle clearance in rats using Freund's adjuvant. As I have mentioned, the initial lung burden may influence the clearance process substantially, and so may the number of exposures. We have seen a dramatic decrease of silica-particle clearance by glucan administration;²³ experimental emphysema due to papain also decreases lung clearance of TiO_2 particles.²⁴ Furthermore, it seems that amosite asbestos preexposure impairs the clearance of TiO_2 particles.²⁵

In regard to delayed clearance of particles from dust foci in the lung, Hatch and Gross¹ maintain that clearance continues even at low rates. In their concept of dust mobilization, edema is supposed to be one of the driving forces. Heppleston²⁶ demonstrated by a double exposure technique, using coal and hematite, that dust foci that do not accompany fibrosis are not static structures. He noticed an intimate mixture of the different particles even when the exposures were six months apart.

CONCLUSIONS

In the attempt to review the basic attributes of particle clearance from the alveoli via the respiratory airways, I have been dealing with that part of lung clearance which depends on the alveolar macrophages coupled to the ciliary-mucous transport process. After the exposure to dust has begun, the onset of alveolar clearance begins within minutes, overlapping in time with the rapid clearance of particles from the tracheobronchial system. The number of macrophages increases rapidly within hours, and their motility is sustained even with a particle load. The way in which these phagocytes reach the ciliary region, however, is not known. After the rapid initiation, the consecutive removal of macrophages with particles from the alveoli is slower than their replacement, so that a buildup, which depends on the amount of dust, occurs. In rats, the retention half time for SiO_2 or TiO_2 particles is about 90 days after a single exposure. Clearance is a function of the initial lung burden, and the cleared amount may substantially increase in accordance with the lung burden. Several

or multiple exposures may change the clearance rate, and so may the intervals between exposures. The efficiency of clearance may be improved by experimental means, but this increase never reaches the order of the initial lung burden effect. As may be expected, experiments have been performed which resulted in a decreased clearance.

The relevance of these findings to coal workers' pneumoconiosis seems to be obvious. At the least, let me point out that single and multiple exposures have different effects on clearance. There is a good possibility that environmental factors may also impair clearance. Practical applications based on our observations are unavailable to date.

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