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Some Aspects of the Problem of Individual Predisposition to Silicosis

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Based on experimental and epidemiological data findings presented here, as well as on data of other investigators, the authors conclude that a wide interindividual variability of susceptibility to silicosis is a real phenomenon. This susceptibility depends on both intrinsic features of the host and the influence of many environmental factors. The effect of any such factor is realized at different stages of silicosis pathogenesis and in close interrelation with the influence of other factors. The necessity of multifactorial analysis is stressed, and an example of such analysis is presented.

Any environmental factor that causes disease, especially an occupational disease, does so because of its qualitative and quantitative characteristics, but also because of certain aspects related to the host organism. These aspects include the ability to resist the injury ("protection," "resistance") and the intensity, or sometimes even the peculiar pattern of a pathological response to the injury ("susceptibility," "vulnerability," etc.).

Silicosis is an occupational disease that has recently drawn much attention, due to the low dust levels that workers are exposed to in the majority of industries in technically developed countries. The fact that only a small proportion of exposed workers contract this disease, even after long-term employment, indicates that there is a "susceptible group" which is sensitive to dust exposures that are harmless to the majority of employees. This observation provides a scientific basis for the implementation of measures which might systematically prevent individuals from contracting the disease by screening out vulnerable persons and defining corrective influences to reduce their susceptibility. These considerations form the basis for studying the problem of individual predisposition or susceptibility to silicosis (*1,2*).

However, even among the individuals who were exposed to high quartz dust levels, a number of them developed the disease after several months or up to three years of employment (so-called early or acute silicosis); others did only after many years of exposure, and still others finished the long-term employment with no signs or symptoms of silicosis (*3*). Even in the late sixties, in the Bolivian tin mines, silicosis or silicotuberculosis was discovered in 24.5% of all workers and in 41.3% of those working underground, which reflected poor work conditions (*4*). Some miners, however, fell ill within the first 5 years of exposure (6.3%), while 57.6% remained healthy, even after more than 20 years of employment.

Differences in outcome of persons employed in the same mine (or a mill, factory, etc.) may result from variations in actual work conditions that are not always self-evident. Individuals may have worked in different areas of the industrial enterprise under consideration or in different jobs associated with varying amounts of dust exposures. For example, when copper miners who had contracted silicosis were questioned in one particular study, they confessed to violating dust control regulations (e.g., switching off the water supply when drilling the first few centimeters of boreholes) more often than their colleagues who had remained healthy (*5*). On the other hand, such exposure differences are not likely to be responsible for all variations. Findings from many studies demonstrated that some workers who developed silicosis had relatively less cumulative dust exposures than those who remained healthy. It appears, therefore, that individual susceptibility to silicosis is indeed not a myth (*6*).

The authors of a recent essay on this problem suggested that individual vulnerability is not connected with a lack of individual resistance, but is rather a peculiar phenomenon; thus, factors of protection and factors of vulnerability should be considered separately (*2*). It is, however, quite possible that, if there is a factor that makes the host more resistant to harmful effects of dust, enhanced vulnerability may result from the absence or quantitative gradation of this factor.

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Some Theoretical Premises of Pathogenesis

The pathogenesis of silicosis involves a complicated and multistage process. It is of interest to consider that the factors causing an individual's predisposition to the disease may operate at a specific stage of the disease. In reality, the stages are closely intertwined, but for the purpose of this study, the process may be schematically divided into three main stages that are regarded as consecutive.

The first of these stages is a lasting dust retention in the lung tissue and the regional lymph nodes. This results from two counterbalancing phenomena: deposition of inhaled particles in low airways and their clearance. A well known estimate of the mass of dust recovered from miners' lungs postmortem compared with the computed dust deposition is approximately 98 to 99% total efficiency of pulmonary dust clearance during a long period of underground work (*7*). This seemingly narrow range indicates that under identical dust exposures, one may expect up to a twofold difference between the masses of dust accumulated in the lungs. The results of an investigation of individual variability measuring the retention of labeled particles after short-term inhalation exposure to test aerosol agree with such an estimate (*8*), while the individual characteristics proved to be quite stable. To a great extent, such differences must affect the development of the pathological process due to accumulated dust. Thus, it would be very interesting to investigate the possibility of the action of susceptibility factors just through an increase (factors of protection or resistance) or a decrease (factors of vulnerability) in pulmonary, mainly alveolar, dust clearance efficiency.

The second stage in the pathogenesis in silicosis is a primary interaction between dust particles and phagocytizing cells, particularly pulmonary macrophages (those of the alveoli and those of the interstitial pool). The damage to the macrophage results in a greater tendency for cytotoxic quartz dust to be retained in lungs and triggers compensatory mechanisms leading to a better pulmonary clearance (*9,10*). On the other hand, it is the same damage to macrophages, due to properties of silica particles not yet fully understood, that serves as a trigger mechanism for enhanced fibrogenesis (*11,12*) and possibly the immunopathologic components of silicosis. However, there is also a hypothesis stating that the immunopathology of silicosis is due to stimulation of the macrophage (*13,14*). Thus, the quartz–macrophage interaction serves not only as a connecting link between the provisionally outlined first stage of the silicosis pathogenesis and its consequent steps, but plays a key role in this process as a whole. Recent findings confirm that a positive correlation exists between the cytotoxicity of different dusts for macrophages and their fibrogenic effect *in vivo*, and also expose the possible causes for some deviations from it (*15*).

The damaging effect from a given dose of the same dust particles to macrophages is clearly dependent on the cell's sensitivity to its action, which is subjected to both individual and group variability. For example, rats exposed to the same quartz dust inhalations vary significantly both in the percentage of degenerated alveolar macrophages in their bronchopulmonary lavages, and in the ratio of neutrophil leukocytes to alveolar macrophages; the latter being an indirect index of cytotoxic effect of the inhaled particle and is connected with the above percentage through a certain equation (*9*). On the other hand, group average values of both indices depend on the sex and age of rats exposed to dust. When peritoneal macrophages obtained from different rats of a certain group were exposed *in vitro* to one and the same dose of reference quartz dust DQ_{12} three times at 30-day intervals, the group average index of cytotoxic effect (as judged by inhibition of the TTC-reductase activity) remained nearly constant, while the individual values fluctuated in every instance with coefficients of variation from 0.3 to 0.4 (*16*). To date, the lack of similar data related to humans is due to reasons that are easy to understand, but there are no biological grounds to expect the absence of some degree of variability of macrophage sensitivity to quartz cytotoxicity in man.*

We believe this variability plays a considerable role in the immediate reasons for the individual predisposition to silicosis. Much experimental data supports this concept. For example, age- and sex-dependent differences in the susceptibility of rats to the fibrogenic effect of quartz dust on the lungs correspond in general to the abovementioned age-sex differences in the sensitivity of alveolar macrophages to its cytotoxicity (*17*). Many environmental factors are able to enhance or decrease the resistance of these cells to quartz cytotoxicity, and more often than not, those factors correspondingly influence dust retention, particularly in lymph nodes, also in the lungs, and additionally, the fibrogenic effect. A similar correspondence between these three phenomena was also observed under the influence of polyvinylpyridine-*N*-oxide (*18*) and glutamate (*19*). Such situations may well serve as a model for correlations resulting from natural variations of the host's reactivity, reflected in the variable sensitivity of macrophage to quartz-induced damage. The previously outlined task to determine a prediction for such sensitivity in humans appears to be still more attractive if one takes into consideration the possibility of such natural correlations.

The third stage in the pathogenesis of silicosis involves a complicated chain of responses to the primary interaction between quartz and the macrophage, including relatively simple, almost direct responses and those that are multistage. The multistage responses are closely connected through cause-effect relationships and

*A test for blood monocyte sensitivity to the cytotoxic action of quartz in standard exposure conditions might serve as a circumventing approach to the evaluation of this variability, but experiments confirming a close enough correlation between such sensitivity and that of pulmonary macrophages to the same quartz dust should be a necessary prerequisite for interpretation of this test.

feedbacks loops involving both cellular and humoral immune reactions. Such a division of responses is not absolute, however. For example, even if the recruitment of new macrophages as well as neutrophils is a relatively simple protective response controlled chiefly by the quantity of products of macrophage breakdown in low airways and alveoli, the level of this response still clearly depends on the neurohormonal background (*10*). The enhanced synthesis of collagen by fibroblasts is a direct response to macrophage destruction due to quartz cytotoxicity; this response is mediated through the formation and/or release of a "silicotic fibrogenic factor" by macrophages and through inactivation of the macrophage RNase which normally controls the fibroblast biosynthetic activity(*11*). However, the possibility of enhancing or partially inhibiting the silicotic fibrogenesis with immunogenic or immunodepressant factors (*20–24*) bears testimony to the fact that the real process is much more complicated and cannot be separated from the immunopathology of silicosis (*14*).

Thus, the variable reactivity of the host (in particular, its immune reactivity, the responsiveness of its neurohormonal control systems, etc.) serves as a prerequisite for the variable susceptibility to silicosis (*25*). It should be emphasized that this construction not only implies a dependence of immediate and indirect protective or pathological responses (referred to as the third stage of silicosis pathogenesis) on this reactivity, but also, its close interconnection with the previous stages. For example, experimental results suggest that an additional relatively weak antigenic challenge can, under some conditions, increase the resistance of pulmonary macrophages to the cytotoxic action of quartz dust *in vivo*, thereby decreasing retention in lungs and the intensity of pulmonary fibrosis (*26*). It is well known that such responses are not observed under other experimental conditions when enhancement of silicotic fibrogenesis predominates, due to stimulation of an immunopathological component of the "third stage" of the process (*20–22*); the same was apparent in the abovementioned experiment in the paratracheal lymph nodes of the rats, while the silicotic process in their lungs was attenuated (*26*). This example illustrates the complexity and poor predictability of the effect of any interference with the third stage of the pathogenesis of silicosis.

In rats exposed to long-term inhalation of quartz dust, the pattern of correlation between initial indices of immune reactivity and the alveolar phagocytosis response as well as the intensity of silicotic pulmonary fibrosis was changed markedly depending on the duration of exposure (*27*). Also, the host's immune reactivity itself may change considerably under the influence of the silicotic process (*28*). These considerations make the predictability of silicosis developing in a person from initial (i.e., pre-exposure) indices of immune reactivity doubtful. One may agree with the allegation that any immunological difference discovered post factum between "the vulnerable" and "the resistant" is a consequence of, rather than a reason for, the development or the absence of silicosis (*29*).

Factors of Individual Susceptibility

The susceptibility of an organism to silicosis-inducing dust is always determined by a complexity of factors, both constitutional and environmental. Since the contribution and importance of any individual factor depends on its own peculiarities and its interrelations with the whole complex, it may exert different effects under different circumstances. Still, the direction in which any individual factor exerts its influence is of considerable scientific interest, since this information is necessary in order to undertake any serious analysis of multifactorial dependence of susceptibility to silicosis. It is reasonable to assume that suceptibility depends on both the host's intrinsic peculiarities (genotype, sex, age) and the influence of some environmental factors that may either accompany the dust exposure (particularly occupational factors) or be separated from it (e.g., nutritional conditions). Some harmful habits and intercurrent diseases may additionally contribute.

Despite the dissimilarity of such susceptibility factors, as well as the complexity and diversity of their effects, they appear to have two principal features in common: the results of their presence is always either an increase or a decrease in the probability of developing silicosis under the same dust exposure; and their influence always involves some of the pathogenetic mechanisms previously discussed. For example, a change in the sensitivity of macrophages to the cytotoxicity of quartz particles may depend on sex (*17*), nutritional factors (*9,30,31*), muscular training (*32,33*), or long-term exposure to low levels of sulfur dioxide (*34*). The significance of this change for the development of silicosis is principally the same in all of these circumstances, irrespective of the factor's nature, although other interactive mechanisms may modulate for an end effect.

Host Characteristics

Individual sensitivity to the action of quartz dust depends on the intrinsic features of a host organism. Even under strictly controlled conditions of equal dust exposure using fairly uniform groups of animals, there are variables in the mass of dust accumulated in the lungs and the pathological lesions that result.

Genetic Predisposition

The possibility of this variability being related to genotype is suggested by the unequal intensity of silicosis development in rats of different inbred strains (*35*). It is much more difficult to estimate the contribution of genotype in intergroup variability of susceptibility to silicosis in genetically nonhomogenous human populations. Even if it were possible to isolate members of a nationality who were employed in the same industrial

enterprise, there are too many differences that remain unknown, such as living conditions, nourishment, etc.

Over the past years, many attempts have been made to show a correlation between individual predisposition to silicosis and the host's genotypic features. The incidence of some "genetic marker"; e.g., the ABO group (*36–38*) or different histocompatibility antigens of the HLA system (*39–43*) were compared in the groups of ill and healthy individuals. For example, up to fifteen different HLA antigens were cited by different authors as associated with a predisposition to pneumoconiosis. No two investigations led to coinciding results, and some failed to show any correlation (*43*).

Sex-Dependent Predisposition

Nearly all authors who conducted investigations comparing the incidence and the time of development of silicosis in men and women who had been working in presumably equal conditions concluded that women are more predisposed to this disease (*13,44–46*). The fact that some characteristics of the male working populations (e.g., smoking, overindulging in alcohol, chronic bronchitis, etc.) tend to increase the probability of developing silicosis seems to provide additional circumstantial evidence in favor of greater sensitivity of females to the harmful action of quartz dust. However, it is impossible to ensure that the actual dust exposures of male and female workers were really equal, since even if individuals work in the same department, they often have different job distributions and/or perform different operations.

Experimental findings demonstrated that young female rats are more sensitive than male rats to the fibrogenic action of quartz dust, either instilled intratracheally (*47*) or administered via inhalation (*17*). In the latter case, a higher sensitivity of alveolar macrophages in females to the quartz cytotoxicity was also observed. In prepubescent rats, this sensitivity was very low with no sex-dependent differences, while aging male rats showed a tendency towards developing more intensive silicosis compared to females of the same age. No sex-dependent difference of susceptibility was found in rats exposed to long-term inhalation of chrysotile asbestos (*48*), although it was found that asbestosis had also developed in female workers of younger age and after a shorter exposure period, compared to male employees in the same mill (N.A. Guselnikova, unpublished data).

The results of long-term inhalation experiment with quartz dust (*17*) are in favor of the hypothesis which indicates that the sex-dependent variability of responses to this dust may be based not only on the different intensity of macrophage degeneration due to quartz cytotoxicity, but also on quantitatively different responses of females versus males to the products of macrophage breakdown (PMB). Even with the same percentage of degenerated alveolar macrophages, "the neutrophil shift" in the cell population of bronchopulmonary lavage fluid is more marked in females than in males. That same difference was found after intratracheal instillation of a standard dose of PMB into rats of different sex. A similar increase of the neutrophil shift in response to PMB administration was observed in male rats after premedication with estrone which apparently acted as a pro-inflammatory steroid, while glucocorticoid premedication acted in the opposite direction (*10*).

Age-Related Predisposition

The experimental data referred to also bear witness to the significance of age on the degree of sex influence in the development of silicosis. It is not possible to use these parameters in extrapolating from laboratory rodents to humans, to say nothing of the fact that age differences in man are often connected with social differences. The ages of rats from the beginning to the end of long-term experimental dust exposures have almost nothing in common with age boundaries of occupational dust exposure in man. Using epidemiological data, some investigators came to the conclusion that the highest silicosis risk is connected with commencing dusty work at a very young age (*49–52*), while others found that such commencement is most dangerous for elderly persons (*53–55*). It is likely that truth lies in both suggestions, although mechanisms underlying enhanced susceptibility to silicosis in the two extreme age groups seem to be different (*1*). In the elderly, susceptibility is probably connected with an increased preexisting respiratory and extrapulmonary pathology, while in the young, it is connected with functional immaturity of the protective responses and mechanisms. It must be stressed that age is considered at the commencement of an occupational dust exposure, but the role of aging on background susceptibility is much more difficult to evaluate since it parallels the increase of cumulative exposure and eliminates the most susceptible persons (therefore contracting silicosis in a shorter time) from the group of those still remaining healthy.

Environmental Factors

Our laboratory's experiments were originally aimed only at the investigation of the combined effects of quartz dust and some of the most commonly accompanying factors of work and the industrial environment (*30–34,56,57,59–63*), including in each instance one of the following: cooling or heating environment, an irritant gas, and long-term muscular exercise (treadmill). In most of those experiments, animals were exposed to dust and to a "non-dust" factor, not simultaneously, but on alternating days. In some initial investigations, the dust was intratracheally administered and followed by a long period of "no-dust" exposure. These patterns of exposures made it possible for investigators to exclude the possibility of any direct interaction of the dust and co-factors under investigation and the effect of the latter on the primary disposition of dust particles during inhalation. The findings indicated changes in the host's reactivity due to the influence of combined effects of

various factors (*63*), and thus led to the recognition of such "non-dust" occupational conditions as real factors in the individual susceptibility to silicosis.

The concept of a "state of nonspecifically increased resistance" (SNIR) developed by a school of Soviet toxicologists and pharmacologists aided comprehension of the experimental findings. This concept is based on experimental evidence and holds that the organism's response to long-term exposure to chemical or physical agents of low intensity involves adaptive and protective reactions which are both specific for each agent, and general with almost standard shifts of host's reactivity. These shifts manifest themselves in the enhanced stability of physiological mechanisms and strengthen the ability of the organism to develop adaptive and protective responses to any other eventually harmful agent, including responses specific for such an agent (e.g., immunogenesis following a vaccination). Of special interest is that the SNIR may be manifested at both the systemic and cellular level, leading to the increase of the *in vivo* resistance of various cell types to different damaging agents.

In the works of this school, much evidence can be found that SNIR-inducing factors include all the above-mentioned "non-dust" factors tested in combination with quartz dust, except heat acclimatization which hinders its development. The SNIR phenomena on the cellular level have been studied most thoroughly via the action of pharmacological inductors of SNIR, particularly some benzimidazol derivatives.* It should be stressed that previous studies did not include macrophages, quartz, or other dust.

All of the mechanisms of the SNIR are not unqualified blessings for the organism exposed to quartz dust. For example, the adverse effect of stimulators of immunogenesis such as Freund's adjuvant (*20,21*), suggests that its stimulation, usually observed under the influence of SNIR-inductors, may be a mechanism that enhances the development of silicosis. In general, the fibrogenesis in pneumoconioses is, in its essence, dust-demarcating, i.e., primarily a protective reaction; however, it is the excess of this reaction that constitutes the main features of the disease under consideration. No wonder, therefore, that just the anti-inductor of the SNIR, i.e., a periodic exposure of animals to high temperatures, was found by us (*57*) and by Bulgarian investigators (*58*) to be a factor inhibiting silicotic pulmonary fibrosis in rats. In another experiment, the same effect had been observed in rabbits, even though they were being exposed to heat and quartz dust inhalation simultaneously and, due to thermoregulatory hyperventilation, retained more dust in their lungs than those exposed to the same inhalations at room temperature.

One might expect the SNIR manifestations on the cellular level to be of considerable beneficial influence in the second stage of the pathogenesis of silicosis, as outlined above. In the course of different experiments where quartz dust inhalations were alternated with training in a moderate muscular exercise, acclimatization to moderate cold exposure (5–7°C, 30 min or 2 hr every second day), or long-term periodic exposure (5 hr per day, 3 days per week) to low levels of sulfur dioxide (mean concentration 47 mg/m^3), one common feature was observed: a marked increase of resistance of alveolar macrophages (AM) to the cytotoxic effect of the engulfed dust particles manifested by a statistically significant decrease of clearly degenerated macrophage proportion and neutrophil leukocytes to AM count ratio (NL/AM) in the cell population of bronchopulmonary lavage (*32–34*). Exactly the same shifts of that cell population were observed when rats inhaling quartz dust were given IM injections of dibazol, a benzimidazol derivative well known as a pharmacological adaptogen. This observation speaks in favor of SNIR as a general mechanism of such effects of the above-mentioned factors of work and environment (*64*).

Taking into account the unquestionably beneficial effect of all those factors on the cell level, each of them differently influences both pulmonary dust retention and the development of silicotic pulmonary fibrosis. Such diversity may be due, not only to the previously mentioned duality of correlation between the SNIR and silicosis development, but also to the fact that all those factors may influence silicosis not only through inducing the SNIR. Moreover, the eventual result of these complicated influences seems to depend significantly on time and strength correlations between agents, i.e., level and aggression of dust challenge on the one hand, and intensity and duration of action of the "non-dust" accompanying factor on the other.

Muscular Activity

Moderate muscular training promoted a decrease of quartz dust retention and some weakening of silicotic fibrogenesis in rats (*33*), while harder training (treadmill running at doubled speed) rendered no beneficial effect on AM resistance to the quartz cytotoxicity, no effect on pulmonary dust retention, and significantly intensified silicotic fibrosis (*30,61*). It seemed logical to explain this intensification in terms of changes in the host's general reactivity which are unfavorable for different processes pertaining to the third stage of pathogenesis of silicosis.† It is interesting to note that rats given a daily allowance of melted fat through a gastric tube as an additional energy resource for accomplishing the same heavy exercise, in addition to their usual diet, exhibited decrease of cytotoxic effect and a weakening of fibrogenesis. The same fat load in rats subjected to no mus-

*In addition to these derivatives, Lazarev's school lists among so-called pharmacological adaptogens, i.e., drugs which are SNIR inductors, different pharmaceutical preparations of the Araliaceae plants (in particular, ginseng, eleutherococcus, etc.), as well as other stimulators traditional for Far-Eastern medicine.

†A similar enhancement of silicotic fibrogenesis had been previously observed in rats under influence of moderate exercise following a single IT instillation of 50 mg quartz dust (*59*). In this case, the role of alveolar particle clearance was minimized due to an overload of dust in the lungs, so evidently the unfavorable influence of SNIR predominated again.

cular training acted conversely. In a worker whose heavy muscular labor is being performed directly in a dusty environment, the principal reason for an increased risk of silicosis may be an excessive deposition of inhaled particles due to markedly increased lung ventilation rather than a change of the general reactivity. The increase in ventilation is due more to a sharp increase of the tidal volume than to breathing frequency (*65*); as shown in a special experiment on volunteers, such a respiratory pattern tends to increase the deposition efficiency of the particles (*66*).

Cold Acclimatization

When rats were exposed to quartz dust intratracheally in one experiment and by inhalation exposure in three others, cold acclimatization increased the fibrogenic effect (*33,60,62,63*). Data obtained by other investigators agree with these results (*58*). A specific peculiarity of the silicosis development on the background of cold acclimatization is that, although the latter gave both indices of increased alveolar macrophage resistance to the cytotoxic effect of inhaled quartz particles (i.e., a decrese in both the degenerated AM percentage and the NL/AM ratio), the total cell count of bronchopulmonary lavage was significantly higher than in non-acclimatized rats under the same dust exposure. On the contrary, the decrease of this count is characteristic of other cases of attenuated cytotoxic effect and can be explained by a self-control mechanism mentioned previously (*9,10*). In rats not exposed to quartz, cold acclimatization had no influence on the bronchopulmonary cell population of lavage. This observation is consistent with a measurable increase in the protective reactivity level according to the SNIR concept (which does not exclude the possibility of some quantitative and even qualitative changes of the host's reactivity induced by adaptogens of a different type). At the same time, however, a reactivity shift is observed which is clearly excessive, as the highly cytotoxic quartz dust itself induces an intensive recruitment of AMs, and especially NLs, into lower airways and alveoli. It has long been known that such inordinate recruitment of cells to the free surface of the acinus creates prerequisites for cellular stasis in the respiratory bronchiole, and thus becomes one of the mechanisms of particle retention instead of clearance (*7*). An increase of such retention was observed with the response of alveolar phagocytosis, and especially the NL recruitment, when hyperstimulated with the prodigiosane (*67*). The same results were observed in cold acclimatized rats (*60,62,63*). The slowing down of quartz dust pulmonary clearance under cold stress was also reported by other investigators (*68,69*).

There is evidence for the stimulation of immune responses (*70*) and for the prevalence of mineralocorticoid function of the adrenal cortex (*71*) in animals acclimatized to cold; both shifts may also enhance the silicotic fibrogenesis. As has already been mentioned, mineralocorticoid hormones are able to enhance NL recruitment in response to intratracheal (IT) administration of PMB; a similar effect was shown when comparing responses to a standard does of PMB in cold acclimatized and control rats.

Thus, acclimatization to periodic moderate cooling along with exposures to high concentrations of quartz dust (ca. 50 mg/m^3) or following IT instillation of a 50 mg quartz suspension (which is a very large pulmonary dust load) creates changes in host general reactivity which are predominantly unfavorable for silicosis development. This appears to be especially true for the first and third stages of pathogenesis, the beneficial influence on the second stage notwithstanding. However, when a dust was far less aggressive (namely, that of bituminous shale) and therefore induced much weaker recruitment of phagocytizing cells into airways as compared with quartz dust (at least at relatively low concentrations tested), that same enhancement of cell recruitment due to cold acclimatization favored the decrease of particle retention in lungs (*72*).

The above-mentioned inhibition of silicosogenesis in experiments with heat acclimatization was not subjected to further analysis as yet, so it is difficult to state the limitations of this effect.

Gas Irritants

When sulfurous anydride inhalations were administered to rats exposed to quartz dust over a 4-month period, a significant decrease in retention and a weakening of fibrogenesis were seen. In other words, the findings were in accordance with the observed enhancement of AM resistance to quartz damage *in vivo* (*34*). There is also some evidence for the stimulating effect of this gas on mucociliary transport in rabbits due to proliferation of goblet cells in the epithelium of the lower airways (*73*). However, when the exposure to SO_2 and quartz dust inhalations lasted for 8 months, all of the favorable effects disappeared and there was even a tendency for fibrogenesis to increase (*34*). Along with a possible transiency of the SNIR effect on the cellular level, one must take into consideration that pulmonary toxicity of any irritant gas may add some lesions and a degree of fibrosis in addition to those from quartz dust. These findings were shown earlier in a long-term (up to 9 months) experiment on guinea pigs. In these animals sulfur dioxide exposures at concentrations from 53 to 79 mg/m^3 also caused a marked decrease of pulmonary quartz retention, which in some of them compensated the additive effect under consideration (*56*).

When an irritant gas and dust are present in the air simultaneously, the situation becomes still more complicated since the former is to some degree adsorbed onto the surface of particles. This interaction is deliberately avoided by the special design of the experiments described above. As it is well known, such a combination can importantly change both the acute and chronic effects of the combined exposure. However, the degree and even the direction of those changes are quite uncertain, depending on the stability of gas adsorption and

on the character of chemical interaction between the gas and the silica surface.

Nitrogen dioxide is of special interest in this connection, since it is the most common companion of quartz-containing dusts after blasting in mines. When tridymite particles were administered intratracheally to rats after adsorption of this gas on the particle surface, it was found that the pulmonary silicotic fibrosis and, even more so, that of regional lymph nodes were significantly decreased as compared with rats injected with control dust. These data favored the hypothesis of decreased cytotoxicity of particles (*74*). Indeed, such a decrease was later demonstrated by other investigators, although for other dusts (*75*).

Nutritional Factors

Data concerning changes of host sensitivity to quartz dust induced by some nutritional factors have already been mentioned. The most striking is a favorable effect of glutamate (*18,19,76*). Previous experiments have demonstrated the beneficial influence of a balanced diet and the unfavorable effects of excessive protein or particularly, fat (*77*). The enhancement of silicotic fibrogenesis due to fat overload (especially fats rich in unsaturated fatty acids) has been repeatedly demonstrated (*30,61,78,79*). This detrimental effect disappears if rats are treated with antioxidants, particularly vitamin E (80), and this can be regarded as circumstantial evidence for the participation of lipid peroxidation in its development. On the contrary, an excess of vitamin C seems to enhance experimental silicosogenesis (*81*). It was also shown that in rats exposed to quartz dust inhalation on the background of additional fat load, the accumulation of a sudanophilic matter in pulmonary macrophages and their degeneration were increased (*30,61,82*). As has already been mentioned, these unfavorable effects are completely lacking when the same fat overload is given to rats subjected to a heavy muscular exercise, which apparently promotes the utilization of the excessive fat (*30,31,61*). On the contrary, a combination of the latter with cold acclimatization proved to have the most unfavorable effect (*62*). There has been but one epidemiological study which has shown that miners consuming an excess of fat with their normal diet developed silicosis sooner than those employed in the same mine on a more balanced diet (*83*).

There is no available information about the influence of alcohol on the development of experimental silicosis, although the well known unfavorable effects on the pulmonary protective mechanisms (*84*) suggest that this influence can also be unfavorable. It was noted that the proportion of heavy drinkers among miners who had contracted silicosis was higher than that found among those who still remained healthy (*85*), and that the average length of employment under dust exposure to the moment of detecting silicosis in drinkers was almost half as long as that of nondrinkers (*83*). In the latter study, a similar distinction between smokers and non-smokers was also found. In an investigation mentioned previously (*46*), however, it was shown that silicosis developed sooner in female workers than in male workers, although there were very few smokers among the former and quite a proportion among the latter; thus, the influence of sex apparently prevailed.

The problem under discussion is rather complicated; on the one hand, the information concerning effects of smoking on the self-clearance capacity of lungs is contradictory and sometimes even testified to a favorable influence (*86*); on the other hand, an increased incidence of chronic bronchitis in smokers is beyond any doubt, while the role of this condition in the development of silicosis is still under discussion (see below).

Thus, evaluating the influence of any individual factor on the susceptibility to silicosis is a complicated task. This is true, not only for real situations in which monofactorial influences are seldom encountered, but for model situations of animal experiments as well.

Accompanying Diseases

The atypical character of lung pathology induced by quartz dust in specific pathogen-free rats (*87*), as well as the enhancement of experimental silicosis development under the influence of different microorganisms (*88–90*), serve as evidence for an important role played by general stimulation of immunogenesis in the pathogenesis of silicotic fibrosis (*14*). However, the epidemiological data concerning the influence of certain human diseases on the susceptibility to silicosis are, as a rule, very contradictory.

For example, there are statements in favor of the silicosis-promoting role of chronic tonsillitis (*54,91*) and against it (*5*); for such a role of rheumatoid arthritis (*54*) and against it (*92*); for the influence of pneumonia (*93*) and against it (*94*). While chronic bronchitis is often regarded as the most important clinical feature of any pneumoconiosis, the question of whether it precedes and promotes the development of radiologically recognizable pneumoconiosis is affirmed by some authors (*38*) and negated by others (*95*).

In very rare cases, tuberculosis may precede occupational dust exposure. It is illegal in many countries to employ tuberculous patients in any job connected with such an exposure. When pulmonary tuberculosis develops on the background of long-term dust exposure, many clinical peculiarities of the disease are so close to those of the silicotuberculosis that even in the absence of a convincing radiological picture of silicotic pulmonary fibrosis, it would hardly be possible to consider the tuberculosis as a condition really preceding silicosis. Therefore, it is difficult to decide whether tuberculosis is a factor in the predisposition to silicosis, based on the epidemiological evidence.

As for other above-mentioned diseases, it is believed that the main reason for contradictions lies in the methodological approaches most commonly used by investigators. Some compare the incidence of silicosis in two appropriately selected subpopulations that differ in the

presence or absence of pre-existing disease under consideration. Others investigate the prevalence of the disease in a group of silicotic patients as compared with matched nonsilicotic controls. They fail, however, to eliminate the dependence of results on many other factors of susceptibility in their complex interrelations which, if not accounted for, may mask the true role of the particular disease.

Multifactorial Analysis of Susceptibility to Silicosis in Humans

Two principal considerations lead repeatedly to the inevitability of a multifactorial analysis in the susceptibility to silicosis: real situations in which one is confronted with the problem of individual susceptibility to silicosis are always multifactorial; and individual factors may influence susceptibility quite differently, depending on the co-influence of another factor (combined effects of muscular training and fat load may serve as a good example of such interdependence).

Although there are many mathematical approaches to multifactorial analysis, the consideration of these lies beyond the scope of this paper, since the goal of the authors is to discuss the available information rather than review the actual methods. Therefore, the following information is confined to the experience of the authors in using a method based on the mathematical theory of pattern recognition (termed "image recognition" by Russian mathematicians).

A cohort of workers employed in an industrial enterprise is sampled and observed retrospectively (e.g., to 1960). Included in the study are all persons who, during the years that followed, either contracted silicosis or remained healthy and survived the entire period of the "retrospective follow-up." A proportion of each group serves as a control, and the cohort that remained is divided into men who contracted silicosis and those who did not, by a computer. The distinction is based on features characteristic of each at the starting point, when all members of the cohort were still free of any radiological sign of silicosis. The discrimination rule elaborated by the computer is used to predict (retrospectively) the fate of persons included in the control part of the cohort. The fact that the prediction achieved no less than 80 to 90% accuracy in all cases testifies to the adequacy of the method. Therefore, the features selected by computer from the offered set of characteristics determined to be a "recognition of image" of a person ill with silicosis did indeed represent significant risk factors (i.e., factors of sensitivity or, on the contrary, protection). Moreover, the method also allows a comparison to be made between risk factors and predisposition to the disease. The correlation between the silicosis risk and the variable values of each factor, or the dependence of the risk on the presence of absence of alternative features is being analyzed.

The features in the set determining the degree of dust exposure include level of particular jobs (e.g., miners working on the rock face versus all other underground workers of the same mine), the length of employment in the jobs, the total duration of dust exposure (including that connected with previous jobs), etc. Features such as these in various combinations and orders usually proved to be the most informative. A prediction based on these features is never satisfactory, however, and this fact alone can provide circumstantial evidence for the important part played by individual susceptibility. It should also be noted that the actual influence of some of these factors is neither trivial nor apriori predictable. For example, an increase in the duration of dust exposure preceding the year of cohort sampling undoubtedly raises the probability of contracting silicosis during the period of "follow-up" initially, and then a decrease is experienced as the time parameter increases. Such paradoxical results are obviously due to the effect of a kind of natural selection, as the group of employees still healthy in spite of a long period of preceding dust exposure (moreover, an exposure to levels higher than those characteristic of modern work conditions) is markedly "enriched" with individuals whose initial suspectibility had been minimal.

It is noteworthy that the predictions proved to be correct in a sufficiently high percentage of controls, despite the fact that features (individual factors) offered for the image recognition could not be considered truly constitutional, with the exception of sex (only for surface industries) and age at the beginning of dust exposure. (If nationality is to be included in that group of factors, it could only be done with great caution and many stipulations.) This result could be regarded as evidence against the importance of genotype among all of the other multifactorial influences on the individual susceptibility; however, it cannot be negated that evaluation of susceptibility would be still more reliable if some of the "genetic markers" mentioned in the previous section were considered as well.

The effect of age at the beginning of dust exposure, as could be expected from the analysis of different authors' data, proved to be biphasic with a minimum probability of contracting silicosis corresponding to approximately 30 to 33 years; the most dangerous age group still included the youngest individuals (less than 20).

The features that proved to be the most informative in predicting the probability of silicosis in workers of several copper mines have been summarized (*96*), using the cohort sampled from the 1960 working population without any signs of silicosis. Among the fifteen features offered, the computer selected twelve as sufficient and necessary for the prediction of probability. This proved to be correct in 94% of controls who had developed silicosis, and in 100% of those who had not. Listed in order of decreasing significance, the twelve factors are as follows: (1) type of underground job; (2) employment in a "dusty" industry before commencing work in the mine; (3) length of work period on the rock face; (4) housing conditions; (5) age when commencing work in a dusty environment; (6) presence of pre-existent

chronic bronchitis; (7) possession of garden, kitchen-garden, poultry, cow; (8) over-indulgence in alcohol; (9) smoking; (10) length of employment in the mine prior to the period of sharp decrease in dust levels; (11) past history of pneumonia; and (12) belonging to one of two main nationalities inhabiting the locality. In considering these factors, it should be stressed that, although significance of the latter feature is arbitrarily expressed as fifteen times less than that of the first, exclusion of any feature makes the prediction markedly less reliable. This implies that any individual factor does not influence silicosis development independently, but rather, in complex interrelation with each other.

The results of an analysis conducted in a large silica-brick plant using the same method are similar, although the comparative contributions of individual susceptibility factors were somewhat different; e.g., chronic bronchitis proved to be of greater relative importance. It is noteworthy that along with this condition, all data confirm an unfavorable influence of smoking and alcohol. An unfavorable role was also played by pneumonia. The easy availability of an additional source of fresh and sound farm products proved to be a factor that predisposed to the lack of development of silicosis; this finding may be regarded as a confirmation of a beneficial role of a balanced diet.

Taken as a whole, the comparison of results obtained in two different industries testifies to the fruitfulness of the method and confirms the necessity of evaluating the actual contribution of any factor to the susceptibility of an individual to silicosis. This contribution must be considered only within the scope of the specific combination in which it is acting.

Conclusion

The interindividual variability of susceptibility to silicosis is dependent not only on constitutional peculiarities of the host organism, but also (and possibly even to a greater extent) on the influence of many different environmental factors and some diseases. The effect of any such factor is, however, variable and sometimes even contrary, depending on the different stages of pathogenesis of silicosis, the strength of the factors, and the time relations to the dust exposure. Still more difficult is the application of experimental data concerning the role of any individual factor to the evaluation of susceptibility to silicosis in real situations where the effects of many different factors are closely intertwined and interdependent. In order to predict the probability of a person working in such a situation to develop silicosis, a complex consideration of a number of risk factors using computerized methods of the mathematical theory of pattern recognition should be recommended.

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