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DAVID A. RYTAND, *Editor*
Stanford University School of Medicine

WILLIAM CREGER, *Associate Editor*
Stanford University School of Medicine

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China clay, or kaolin, is a degradation product of granite and consists of up to 25 per cent of free silica mixed with hydrated aluminium silicate and traces of other elements. A post-mortem examination of a man who had long been exposed to ball clay dust has been described by Thomas (29), who found silicotic nodules which were less whorled than is typical and had taken a very long time to develop; another case, also of long exposure, is given by Bastenier (30). A survey of 31 pottery workers by Chiappa & Ferri (31) disclosed only a relatively benign silicosis. The exposure of rats to the dust by intratracheal injection of saline suspension by King *et al.* (32) revealed only phagocytosis with no fibrosis within periods of 60 to 161 days. The free silica content of the kaolin was not determined, but the silica solubility was very low. It seems that kaolin is definitely not responsible for a fibrous silicosis, like quartz, and that cases in which fibrosis has been observed are a result of tuberculous involvement (30, 33) of lungs heavily charged with dust, or to the presence of quartz with its action modified by the kaolin which does not, however, inhibit the growth of fibrous nodules.

The comparative freedom from silicosis of men in the brick and tile industry, handling china clays and fireclays containing free silica, is commented on by Uytdenhoef (34). They inhaled dust containing 11 to 46 per cent of free silica in concentrations up to 700 particles per cc. He suggests that the concentrations might have been below the danger level or that the aluminium silicates had an inhibitory effect. Size-selective sampling with determination of free silica in the respirable fraction should have been employed.

Deaner (35) describes silicosis in fireclay miners with histological examination of one case. The man had worked for 23 years as a fireclay miner in a colliery where the clay was adjacent to the coal seam. The clay was mainly aluminium silicate with only traces of iron, calcium, potassium, and sodium, but it contained a substantial amount of free silica. Laminated fibrous nodules of classical silicosis were present in the lungs. The occurrence of silicotic nodulation in this case and that of Thomas (29) argues against a specific inhibitory action by colloidal aluminium silicate which appears, on its own, to cause an inert dust type of pneumoconiosis.

Fuller's earth, another clay, is a hydrated alumino silicate containing iron. It has been reported as causing pneumoconiosis (36, 37, 38). Quartz was present in these cases, but the disease differed from classical silicosis and and took longer to develop. The dust contains 50 to 60 per cent of combined silica, i.e., SiO_2 in silicates.

A number of cases of silicosis, diagnosed by chest x-rays, are described by Rombola & Guardascione (39) in the bentonite industry; there had been very heavy exposure to dust. This clay is mainly montmorillonite; it contains a trace of quartz along with 32 per cent of amorphous silica plus beta-cristobalite. There were no post-mortem findings to indicate whether the disease was correctly described as silicosis, exemplified by the classical nodulation, or whether there was diffuse fibrosis and to what extent. The maximum exposure was seven years. A dust containing 32 per cent of free

crystalline silica, inhaled in the concentration and particle size described, would normally have been lethal in this time.

Peretti & Occella (40) suggest that the fibrogenic action of quartz is enhanced in the presence of certain clay hydrosilicates. There appears to be no evidence for this statement, either on physical, chemical or clinical grounds. The rapid onset of silicosis leading to death within a few years, which was common in the days before precautions were taken, among men quarrying sandstone, shaping it, or grinding upon dry sandstone wheels, has no parallel in the exposure to silicates in clay or crystalline form, even when an appreciable amount of free quartz is present. The evidence is towards a diminution of the activity of quartz, attributable rather to the presence of an inert diluent than to specific inhibitory action. Pneumoconioses caused by inhaling dust from clays are essentially slow in developing, even under quite dusty conditions.

Occella (41) has analysed many industrial clays and has found free quartz present in proportions up to 50 per cent. This figure did not always provide a good index of the hazard likely to be attributable to the material, because a low concentration of quartz was often associated with a high proportion in the finer particles, which alone were small enough to be retained in the lungs.

A survey of the cement, clay, and pottery industries by Sayers *et al.* (42) showed the main hazards to be the well-known ones attributable to silica and lead. A study by Parmeggiani (43), based on mass radiography of workers in the cement industry, proved that the highest incidence of pneumoconiosis was amongst those employed in mines and quarries where raw materials were obtained and cement dust was absent. Few workers in the factory where cement was made showed more than slight lung shadows. This was confirmed by Giulani & Belli (44), who x-rayed 180 people working in a cement factory and found no cases of silicosis, although 20 per cent of them gave indications of inert dust deposits. Upper respiratory disturbances were prevalent confirming that industrial hygiene practice should not be restricted to eliminating fine, respirable dust. Russell (45), also, observed the tendency of cement dust to cause bronchitis but found no encouragement of tuberculosis and only slight pneumoconiosis.

Experiments in which rats inhaled dust of Portland cement containing less than 1 per cent of free silica revealed no fibrotic changes (46). Miller & Sayers classed Portland cement as an absorptive dust when tested by peritoneal injection, since the initial lesion dispersed and the dust disappeared (103).

Nonfibrous Crystalline Silicates

Passing on to the crystalline silicates, several papers have been published on exposure to dust of the felspars. These comprise two similar groups of hydrous alumino-silicates of alkalis and alkaline earths crystallising isomorphously in monoclinic and triclinic forms.

Experimenting by the intratracheal injection into rats of dust suspensions in saline, Mohanty *et al.* (47) found that felspar was very much less fibrogenic than quartz. Policard & Collet (48) confirmed this work; they compared three kinds of felspar and obtained varying amounts of fibrosis, increasing with time but always less intense than was produced by silica. Their technique was the intraperitoneal injection of saline suspensions. Klosterkötter & Jötten (49), using intratracheal injection, found only slight fibrosis from a potash felspar; hornblende, another complex crystalline silicate, gave none.

Rotter & Gärtner (50), describing a fatal human case with extensive tuberculosis, state that the nodules were not like those of silicosis, being more widely disseminated; there was also less increase in reticular fibres and collagenous tissue. The dust inhaled by the victim contained 38 to 45 per cent of quartz with many particles smaller than 5 μ; they supposed the aluminium, potassium, sodium, and calcium ions, which would leach out into solution, had exerted a neutralizing effect.

Granite consists of about two-thirds felspar with one-third quartz and mica; it contains small amounts of iron, magnesium, calcium, etc. Silicosis with nodulation is produced in men exposed to the dust, but there is more tendency to diffuse fibrosis than with straightforward silicosis. The condition is progressive and associated with tuberculosis, which causes the deaths, but a much longer exposure is required than would be the case with pure quartz dust. These conclusions were reached following exhaustive studies of granite workers in Vermont (51, 52).

A survey of 355 stonemasons in Australia who worked on sandstone (90 per cent free silica), granite (30 per cent free silica), and limestone (non-siliceous) revealed seven cases of silicosis in sandstone workers and one in a granite mason. Seventy-nine cases of moderate, diffuse fibrosis were seen, without incapacity, and the amount of lung damage was judged to be proportional to the free silica content of the stone worked (53).

In France exposures of up to seven years to very high concentrations of granite dust, produced while tunnelling through rock containing 18.4 per cent of free silica, failed to cause silicosis (54). Surveys of the Austrian and German granite industries led Röhrl to conclude that compensatable silicosis was caused only after breathing the dust for many years (55). Experimenting with rats by intratracheal injection of saline suspensions of Cornish granite dust, King *et al.* produced focal nodulation in 100 days. The nodules, however, contained only a tangled reticulin network without collagen and did not progress up to 250 days (56).

Kaolin is derived from granite, and reviewing the evidence relating to kaolin, felspar, and granite together, it is fairly clear that these substances produce silicosis when inhaled as dusts by virtue of their content of free silica. It is also very doubtful if any inhibitory action can be ascribed to these minerals in respect of the fibrogenic property of free silica. There is no doubt that fibrous nodulation in human lungs results from the inhalation of the dusts and that the aluminium silicate which they contain does not prevent

it. Some degree of modification of the nodule, the presence of diffuse fibrosis, and the long duration of exposure required all seem factors which can be accounted for by the dilution of active siliceous dust by inert silicates.

A method of assessing the silicosis risk attributable to dust made from a particular rock was proposed by Landwehr (57). A danger figure was attributed to each mineral constituent of the rock and multiplied by the weight present. The products for all the constituents were then summed, and the total was multiplied by a fraction representing the percentage of fine dust generated by drilling. No account was taken of constituents which could suppress fibrogenic activity, nor of the fact that the "danger" of a mineral might be a result solely of its quartz content; felspar, for example, was rated as 70 per cent as dangerous as quartz. A scheme of this nature suffers from the limitation that the effects of quartz are different from those of other rocks, which makes it rather misleading to classify them together. Landwehr's treatise contains useful information about a number of rocks.

The olivines, orthorhombic silicates of magnesium, and ferrous iron appear to provoke little fibrosis in the lungs. Experiments on rats by King *et al.* (58), using intratracheal injection of saline suspensions, revealed phagocytosis with the alveolar walls thickened because of congestion of the lymphatics by dust containing macrophages. Slight fibrosis was present in the alveolar walls, but there was no organized focal nodulation. These minerals are used as a substitute for siliceous sand in various industries and have contributed to the decline of silicosis.

Sericite, a muscovite or potash mica, is an alteration product of felspar. Some historical interest attaches to sericite because Jones (59) claimed that it was the cause of silicosis. His argument was based upon his discovery in the lungs of silicotic miners of large numbers of fine needles of sericite under 2 μ in length; quartz particles were also present but in numbers subordinate to sericite. Evidence against this theory was put forward (60 to 63), and both Lemon & Higgins (64) and King *et al.* (65) found that sericite produced a minimal tissue response when injected into rats' lungs; appreciable fibrosis was evoked if the dust was treated with hydrochloric acid before injection though anomalies between solubility and pathological effect were observed. Landwehr (66) claimed sericite to be harmless on its own but to act as a catalyst and to enhance the danger of quartz; his evidence for this statement is not clear. Support for Landwehr's hypothesis is found in papers by Weiland (67) and by Hurlbut & Beyer (68). The experiments of the former, on guinea pigs, seem to have been confused by intercurrent disease. The latter compare two foundries, one with many cases of silicosis and the other with none. While associating the disease with the sericite content of a parting powder used in the bad foundry, and even commenting on the fact that the castings which it turned out possessed a finer finish than those from the other, they entirely fail to record any details of the fettling processes or measurements of dust concentrations during this operation, which was obviously prosecuted more vigorously in the foundry with the high incidence of

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disease. The fettling of castings is the principal cause of silicosis in foundries. It is difficult to credit the theory of Hass (69) that sericite is formed out of quartz within the lungs.

An examination of men working with mica and pegmatite (a mixture of quartz and felspar with some mica) by Dreessen *et al.* (70) revealed true silicosis only amongst men exposed to quartz, though effects were seen that could be ascribed to mica dust. Silicosis has been reported in the Bihar mica mines, but this was probably a result of free silica which was present in rock drillings to an extent between 11 and 67 per cent (71).

Sericite and mica frequently accompany silica in silicotic lungs and other dusts in pneumoconiotic lungs, and it is improbable that any appreciable inhibitory action can be ascribed to them. This view is supported by experience in the slate industry where the danger of the dust is probably attributable to the silica content and is not greatly influenced by associated sericite and mica. The first work on exposure to slate dust in Wales, where the silica content is high (35 per cent) and there is a long history of tuberculosis, was carried out by Wade (72). Silicosis was detected in Australian slate quarries where the free quartz content was 33 per cent (73). In France, however, workers in slate which had a free silica content of only 7 per cent, the rest being largely sericite, showed few signs of respiratory impairment (74). Italian slate also contains a low percentage of quartz, ranging from 2.8 to 8.6 per cent. X-ray photographs of personnel engaged in working Ligurian slate revealed initial signs of pneumoconiosis after 10 to 15 years' employment; silicosis and tuberculosis existed only in men who had retired (75). The diseases had thus required a full working lifetime for their development.

The suggestion that micaceous minerals are liable to cause pneumoconiosis because the particles are flat lamellae does not seem to be borne out by an exaggerated incidence of disease or by a particularly rapid rate of development of disease amongst persons exposed to mica dust. There is certainly no gross effect comparable with the vicious attack from crystalline quartz dust. This suggestion has, however, been made by Landwehr & Bruckmann (76) on the basis of a lack of quartz and an excess of mica and talc platelets in lung sections seen under the microscope. Their result may be accounted for by the small difference between the refractive indices of quartz and Canada balsam which makes the identification of small quartz particles in Canada balsam mounts a difficult matter. Any estimate by visual microscopy of the lung content of dust in particles of the order of 1 μ in size must be subject to considerable uncertainty.

Fibrous Crystalline Silicates

Many silicates crystallise in fibrous form, both as short spicules and in longer fibres; the latter may be either brittle or else silky and flexible, like asbestos, the fibres of which also possess the property of cleaving longitudinally an indefinite number of times.

Sillimanite, an anhydrous aluminium silicate used for special purposes in

the pottery industry, crystallises in hard acicular crystals which do not cleave but are readily ground to powder. Middleton (77) stated on limited evidence that the dust did not appear to be highly dangerous, but it was later held responsible for lung fibrosis, including nodulation, in men engaged in making artificial corundum by heating bauxite and kaolin in an electrical furnace (78, 79).

When rabbits were exposed to airborne sillimanite dust, fibrosis of the lungs with some nodulation was observed (80). Other reports of bauxite fume pneumoconiosis suggest that it is caused by the inhalation of extremely high concentrations of colloidal silica aerosol and that the presence of sillimanite in the fume is incidental. The end result, in these cases, was diffuse, interstitial fibrosis without nodulation, deriving from interference with the koniophage clearance mechanism by the large quantity of dust present in the lungs and the high solubility of colloidal particles of silica (81 to 84). King *et al.* (85), however, have produced a dense, collagenous fibrosis in the lungs of rats by administering large quantities of colloidal alumina (Al_2O_3).

Sepiolite, or meerschaum, a light hydrated magnesium silicate resembling cuttle-fish bone and containing both fibrous crystals and amorphous material, has been cited in one case as a cause of "silicatosis" (86); the x-ray pictures show diffuse shadowing.

The association of the shape of inhaled dust particles with disease is particularly interesting in the case of talc, a hydrated magnesium silicate forming monoclinic crystals which are soft and cleave into small scales and spicules.

Dreessen & Dallavalle found that Georgia talc, a hydrous magnesium silicate containing 20 to 30 per cent of dolomite and 10 per cent of tremolite, was more injurious than tremolite talc (87, 88), though the damage caused was in no way comparable with that attributable to silica dust. The Georgia talc contained many fibrous splinters and aggregates and was composed of hydrous magnesium silicate. Tremolite is a hydrous calcium magnesium silicate which occurs both as slender, blade-like prisms and as silky fibres.

Hogue & Mallette (89), after examining rubber workers exposed to pure talc containing neither fibrous varieties nor free silica, decided that this substance did not produce pathological changes in the lungs, but emphasized that the term "talc" was used commercially in a wide sense to include tremolite, pyrophyllite, and even quartz. Massive lung shadowing in miners of pyrophyllite, a hydrated aluminium silicate similar to talc and occurring in foliated, lamellar and somewhat fibrous masses, was observed by Eason *et al.* (90), but the dust contained from 25 to 35 per cent of free quartz. Porro *et al.* (91) found pneumoconiosis in tremolite workers whose lungs exhibited fibrosis and contained talc bodies resembling asbestos bodies when examined post-mortem. That the fibrous varieties of talc produce a disease analogous to asbestosis, with diffuse fibrosis and asbestos bodies, is confirmed by Siegal *et al.* (92) and by Greenburg (93).

Several other cases of pneumoconiosis, caused by long exposure to talc dust and diagnosed by x-ray as differing from silicosis, have been reported without reference to the shape of the particles (94 to 99). Millman (100) describes a generalized pneumoconiosis from exposure to talcum powder dust which contained less than 0.5 per cent of free silica and was entirely free from the sharp spicules found in the fibrous variety of tremolite talc. There had been 24 years' exposure, a long period, to high dust concentrations, which, with the x-ray reproduced, suggest this to be a case of inert dust pneumoconiosis.

McLaughlin *et al.* (101) made a very thorough examination of the lungs of a worker in a rubber tyre factory who died of rheumatic endocarditis. Although the Norwegian talc dust to which he had been exposed for 33 years contained both platelet and fibrous particles, only the latter, up to 10 μ in length, were recovered from the lungs. Fibrosis was not observed in the root nodes but was scattered throughout the lung in small nodules, more numerous in the lower lobes, which were less compact and lacked the characteristic pattern of silicotic nodules. These nodules were packed with fibrous particles and contained "curious bodies" somewhat similar to those found in cases of asbestosis. There had been no exposure to asbestos.

Rapid development of talc pneumoconiosis, clinically and radiologically similar to silicosis, in workers exposed to very heavy concentrations of dust is described by Alivisatos *et al.* (102). No free silica was present. Dust counts up to 1,925 particles per cc. are quoted; this would not be adequate to account for pronounced x-ray shadowing in periods as short as 16 to 60 months unless a fair proportion of long, fibrous particles was present. No information is given on this point.

Miller & Sayers (103) obtained only an initial foreign body reaction following the intraperitoneal injection of talc (75 per cent fibrous tremolite) and soapstone (65 per cent fibrous tremolite) dust into guinea pigs and, therefore, classed them as inert, while Policard (104), exposing rats to airborne talc dust which contained needle-shaped particles, observed only bronchial reactions and loss of mobility of phagocytes. No fibrosis was found, but the animals were killed off after 20 days which may not have been long enough for it to be recognised. In the human subject talc granulomata of the skin and peritoneum have been described (105 to 109).

Asbestos shares with quartz the capacity for producing rapidly, in a few years, a high degree of fibrosis of the lungs when inhaled as airborne dust. The disease, asbestosis, was first recognised in 1906, and an inquiry into its occurrence was held by the Factory Department of the Home Office in 1928 (110). Its association with tuberculosis is infrequent, compared with silicosis, though this is less marked in England than in the United States and Germany (111). Persons affected with asbestosis have an increased risk of contracting cancer of the lung (112, 113), a tendency which has not been observed with other pneumoconioses (114, 115, 116).

Asbestosis differs from silicosis in additional ways. It does not progress

after exposure to the dust has ceased, and it is characterised by diffuse x-ray shadowing as a result of pulmonary fibrosis which, unlike silicosis, chiefly affects the bases of the lungs, spreading to the middle and upper parts as the disease advances, with the apices usually clear. The laminated, fibrous nodules of silicosis do not grow as a result of the presence of asbestos in the lungs; instead, a diffuse, general fibrosis without calcification is stimulated.

Characteristic asbestos bodies are found in the fibrous tissue, air spaces, and sputum and within macrophages; they consist of asbestos fibres sheathed with iron-containing protein derived from the capillary exudate. They were first observed in the lungs of an asbestos worker in 1927; similar objects have since been found in cases of talc, graphite, carborundum, and coal pneumoconiosis and, possibly, byssinosis. Asbestos bodies may be up to 250 μ long; ultimately, they appear to break up and disperse (117, 118, 119). Injection of asbestos bodies into the peritoneum of guinea pigs failed to provoke the fibrous reaction observed with naked fibres (124); Miller & Sayers (103), however, found asbestos fibres to be inert by a similar technique.

Asbestos fibres produce granulomata of the skin, or asbestos corns (120, 121, 122), which do not contain asbestos bodies. An immediate inflammatory reaction in the peritoneum of mice has been caused by fibres detached accidentally from an asbestos sterilizing filter; talc acted similarly, but glass fibres and mica produced only a slight response with no immediate effect from silica (123), possibly because the particles were too coarse (140 mesh)

Histologically, the characteristic feature of asbestosis is the growth of fibrosis around the fine bronchioles and alveolar ducts, suggesting that asbestos fibres lodge across air channels which are of appropriate diameter and work into the surrounding tissue by virtue of its movement during respiration. This has been supported by the results of many animal experiments at Saranac by L. U. Gardner which have been reported by Vorwald *et al.* (124). These showed that peribronchiolar fibrosis could be produced in guinea pigs, cats, and rats by inhalation of asbestos dust containing fibres around 10 μ in length. No effect was produced in mice. Inhalation of dust almost free from long fibres produced little fibrosis. Further experiments by intratracheal injection of long and short fibre dusts, using various kinds of mineral, were carried out. Using fibres 20 to 50 μ long it was shown that chrysotile, amosite, crocidolite, tremolite, and brucite were active; for some reason anthophyllite was not. Brucite is a fibrous form of magnesium hydroxide which is free from silica. Glass wool, of the same length and 3 μ in diameter, produced no fibrosis. When the dusts were ground before administration, so as to break up the long fibres into pieces 3 μ and less in size, no fibrous reaction was produced by any of them; the only effect observed was a greater or lesser inflammatory reaction with transport by phagocytes to the lymphatics.

The association is with the fibrous habit of the mineral, not with its crystalline form; chrysotile is probably rhombic, amosite is orthorhombic, crocidolite and tremolite are monoclinic, and brucite belongs to the rhombohedral section of the hexagonal systems. Anthophyllite is orthorhombic.

All these minerals, because of an enormously exaggerated rate of crystal growth along a particular axis being encouraged by conditions at the time of their formation, may occur in the form of long fibres which are capable of repeated longitudinal subdivision. It is this growth habit which Vorwald and his colleagues correlate with the power to produce asbestosis; non-cleaving fibres of glass of similar length do not cause the disease. Vorwald and his co-workers clinch their argument with observations following intravenous and intraperitoneal injection.

Quartz particles below 3 μ in size, when injected into the veins, collected in various organs, such as the liver and spleen, and caused the growth of hyalinised fibrotic nodules of characteristic type. The asbestos minerals, ground to particles shorter than 3μ, produced no effect. Intraperitoneal injections of the short fibre dusts caused only the phagocyte reaction commonly excited by inert dusts, with no fibrosis. Long fibre asbestos minerals, including anthophyllite, gave rise to fibrosis.

It is also claimed that direct injection of long asbestos fibres into the spleen did not cause asbestosis because this organ is static, whereas the lung and peritoneum are mobile, which makes the ends of the fibres work into the tissues. Full details of this experiment are lacking from the paper.

Further evidence in favour of mechanical, rather than chemical, action is afforded by their observations that colloidal aluminium hydroxide did not inhibit asbestosis, while King *et al.* (125) found, similarly, that metallic aluminium had no inhibitory effect. These substances prevent fibrosis from quartz (126, 127), although an exception has been mentioned by King (128).

Observations on the disease in humans confirm the existence of a mechanical factor in its origin. A typical case is described by Luton *et al.* (129) of asbestosis in a man who died after 18 years' exposure to concentrations of particles up to 4,000 per cc. containing fibres up to 10 μ in length. There were no localised nodules in the lungs, but a general thickening of the pleura in the lower parts of each lung was evident. Many asbestos bodies were seen, isolated and in groups, and dust particles could be traced, not only in the lungs, but also in the vessels of the liver, kidney, and spleen.

Cartier, describing conditions at the Thetford mines in Canada (130), states that all cases of asbestosis arose from exposures of over 14 years' duration to concentrations exceeding 18 particles per cubic centimetre of chrysotile asbestos fibres, which were dry, partially cleaved, and from 10 to 250 μ long. This concentration is of the order of one-tenth of what would be required to cause silicosis from quartz dust, and less than one-hundredth of the figure associated with an inert dust pneumoconiosis in the same period of exposure. Other dust, consisting mainly of powdered serpentine rock, appeared to be harmless.

Asbestosis from Finnish amphibole, a hard, brittle variety, is described by Noro (131). Fibres and asbestos bodies were found in the lungs of victims, the fibres being mostly 9 μ or less in length and under 1 μ in diameter; a few fibres up to 65 μ long were seen.

Dreessen *et al.* (132), in an exhaustive study of an asbestos textile in-

dustry, where the risk of asbestosis is much greater than in mining, found airborne fibres of a median length ranging from 7 to 163 μ. Asbestosis was diagnosed in many workers and asbestos bodies were found in the lungs. Dreessen and his colleagues comment on the very low dust concentrations which could be held responsible for causing the disease. Concentrations below 180 particles per cubic centimetre, measured with a Konimeter, were suggested as being safe; as no attempt was made to distinguish between fibrous and nonfibrous particles, this does not necessarily conflict with Cartier's figure given above. The asbestos was mainly chrysotile.

Alden and Howell (122) describe corns produced in 99 out of 167 workers with amosite. No asbestosis was detected, but figures for the airborne dust concentration are not included.

These facts do not oppose the theory that asbestosis is caused by fibres penetrating the tissue of the primary lung lobule, in the airways of which they are held up on account of their length; it is also conceivable that easy longitudinal cleavage of the fibres, which results in fraying of the broken ends, may be a necessary physical factor additional to a length exceeding 10 μ. In spite of the failure of aluminium to inhibit fibrous growth, however, the possibility of a specific chemical reaction at the ends of the fibres cannot be excluded.

Asbestos bodies provide visual evidence of chemical action against the invading fibres, probably to render them innocuous, with special activity at fractured ends. The ultimate development of cancer cannot readily be accepted as resulting from mechanical stimulus, or the presence of fibrous tissue, without postulating some accessory cause. The asbestos corn, stimulated by small slivers penetrating the skin of the hand, under which a fibrous response is initiated, seems to be more specific than a foreign body reaction. The handling of glass wool, slag wool, and even glass fabrics causes skin irritation because of the pentration of glass fibres, but corns are not produced, nor is there evidence of pneumoconiosis, although long exposures have not yet been recorded (133, 134, 135). Finally, Kettle (25) injected ground asbestos into subcutaneous connective tissue and produced active lesions, like those attributable to silica.

In considering the reaction of tissue to dust, both the immediate inflammatory reaction, and the long-term, fibrotic effect, have to be differentiated. Regarding the latter, asbestos and talc dusts appear to be selective in respect of both the organ and the species of animal, which is not the case with quartz. Quartz dust provokes a fibrogenic reaction, with only minor differences between species, in every organ capable of retaining particles and in every kind of animal which has been investigated (136, 137).

Miller & Sayers (103) found no fibrosis in guinea pigs injected intraperitoneally with asbestos and talc. Gardner (136) obtained only a very slight effect in the lungs of mice and dogs with asbestos while man, guinea pig, cat, and rat developed fibrosis. He inoculated the dog by intratracheal injection of a suspension of long chrysotile fibres in saline which failed to produce more

than minute granulomata in peripheral lymphoid tissue, although observation was continued for two years. Inhalation was employed for the mouse; asbestos bodies were formed, but the tissue response remained limited to phagocytosis over a period of two years.

Yet the dog can experience asbestosis, for Schuster (138) describes one which had inhaled dust for 10 years in a factory where three kinds of asbestos were handled. The lungs contained fibres from 8 to 60 μ long, and there was considerable diffuse, interstitial, peribronchiolar, and perivascular fibrosis. Asbestos bodies were absent.

These variations in the response to asbestos fibres are peculiar, and it is doubtful if they are genuinely a result of differences of susceptibility. For fibrous growth to be initiated, contact must be established between the stimulating agent and an area of connective tissue. It is conceivable that this contact is mechanically uncertain in the case of long fibres, especially when they are administered by the injection of a liquid suspension; more uncertain than is the case with granules of quartz.

The relationship of the immediate inflammatory reaction, which is often produced by the injection of foreign material into tissue, to the long term fibrosis also requires consideration. Kettle (139) describes a tissue response to subcutaneous injections of colloidal silicic acid which included necrosis and the ultimate development of a fibrous scar. He also produced similar lesions from the solution of silicic acid which leached out of a permeable collodion bag of silica embedded in tissue.

It is doubtful if these lesions can be regarded as analogous to the proliferating silicotic nodule. Gardner, Miller & Sayers, and other more recent experimenters, disregard any initial reaction and concentrate on the growing nodule, which is evident only after a period of weeks. Kettle's asbestos lesions referred to above (25) may come into the same category as his silicic acid scars.

Complete disregard of the variable initial reaction seems unjustified, at least in the case of asbestos, because it is doubtful if asbestosis in humans is progressive. There may be a similarity between the asbestos scar in the connective tissue under the skin, and the lung condition of asbestosis.

Physical and Chemical Factors in Pneumoconiosis

The difference between silicosis and asbestosis arises from the physical difference between the two dusts which cause them. Silicotic nodules are focal collections of large numbers of particles which have been gathered together from the distributed sites of their original deposition upon the walls of the air spaces in the lungs. The focalisation is a result of phagocyte activity and lymph currents, and it is necessary to postulate that the silica particles cannot harm the phagocytes appreciably if this description is accepted.

It is physically impossible for a long fibre, over about 20 μ, to be engulfed by a single phagocyte; hence the building up of focal aggregations of such

particles cannot take place, and the fibrosis which they produce must be diffuse.

Normally, particles over 5 or 10 μ in size are not admitted to the fine bronchioles and alveoli, since they impinge or settle under gravity upon the ciliated walls of the bronchi and bronchioles and are excreted. Fine fibres have a much greater ratio of surface area to weight than compact granules. Hence the viscous drag of the air upon their surface, which is set up when they move relative to the air, is abnormally large. They possess, therefore, a strong tendency to travel with an air stream, which explains the occurrence in lung tissue of asbestos fibres up to 250 μ long.

Asbestosis has been described as a disease of the primary lobule with silicosis as a disease of the lymph node. It is correct to go beyond this generalisation and say that both are diseases of connective tissue. The fibrosing agent must establish contact with tissue capable of producing collagen fibres. In the case of asbestosis, this is the lymphoid tissue of the primary lobule, the distribution of which has been described by Miller (140); in the case of the asbestos corn it is the connective tissue beneath the skin. In experimental pneumoconiosis it is the connective tissue of the organ inoculated with fibrogenic particles.

The inhalation of asbestos dust results in the accumulation in lymph nodes of all particles small enough to have been phagocytosed. Mild fibrous reaction has been observed from these. The long fibres are caught in the primary lobules and produce local fibrosis. The case of talc fibrosis reported by McLaughlin *et al.* (101) seems to be intermediate between the complete focalisation found with quartz dust and the complete diffuseness of asbestosis, attributable to fibres exceeding 20 μ in length. Small, scattered nodules, poorly defined, were seen which contained talc fibres up to 10 μ long but which were mainly between 4 and 5 μ. This length is probably the greatest which can be transported, and the small size, poor definition, and large number of nodules may reflect the growing difficulty of transport as the fibre length increases above 5 μ.

The electron microscope has revealed that connective tissue contains a sub-microscopic network of collagen fibrils along with intercellular material and fluid and fibre-forming cells (141). The mechanism by which the cells make fibres is not yet clear, but cytoplasmic fibres and granules (142), containing an acidic polysaccharide-protein complex, are involved and may precipitate the fibres extracellularly by a process controlled by van der Waals and electrostatic interactions with neighbouring molecules (143).

Fibres of collagen carry periodic markings having a separation of about 640 A and are similar, irrespective of their biological origin, a fact which correlates with the unspecific nature of experimental silicosis and suggests a growth mechanism common to all species.

It is still obscure how the presence of silica particles in connective tissue can stimulate the fibrogenic cells to produce collagen at an abnormal rate. The resulting nodules are similar to those of tuberculosis (144), and there

must be some feature in the chain of causation common to the crystal of quartz and the tubercle bacillus. The association of tuberculosis with dusty occupations was observed before the identification of silicosis, and the experimental increase of the local reaction to tubercle bacilli in the presence of colloidal solution of silica, itself toxic (145), is well established (146, 147).

Gye & Purdy (145) showed that the tissue change induced by silica sol administered parenterally consisted of a slow thickening of capillary boundaries by a deposit of collagen, and their work encouraged the theory that solution of silicic acid from quartz particles in the lymph tissue initiated fibrous growth. It could equally well be argued that silica would be precipitated from the colloidal solution owing to its particles aggregating at the low pH of blood and, depositing in the connective tissue irrigated by the capillaries, would initiate collagenous growth near their walls.

This view persisted for 30 years in spite of certain difficulties. Banting (148) was one of the first to distinguish clearly the peculiar nature of the growing silicotic nodule as distinct from the local toxic action, necrosis, and formation of scar tissue which followed the injection of colloidal silica sol. He showed that nodules could be produced only by particulate silica; in addition he repeated Kettle's experiment of implanting a permeable bag of silica into tissue and failed to obtain nodules. Banting's conclusion was that particulate silica caused silicosis and that fibrosis might be initiated by the phagocyte changing from an amoeboid to a connective tissue cell.

The solubility theory persisted, nevertheless, with support from the observed decrease in silica solubility caused by the presence of small amounts of iron (25) or aluminium and of larger quantities of calcium hydroxide or cement (126, 127), or by the presence of other rock dusts (128).

There was some evidence of a parallel diminution of fibrogenic action, though exceptions were noted. Reports of siliceous dusts which were failing to produce silicosis were accounted for by the assumption of a depression, by another constituent, of silica solubility, as mentioned previously, and were accepted as evidence in favour of the solubility theory.

It was also found that the fibrogenic effects of certain silicates ran parallel with their solubilities (154); the weakness in this argument lies in the indirect and unspecific association between the dust administered and the resulting fibrous growth, except in the case of free silica.

The grounds for believing that silicic acid, dissolved from particles of silica and silicate by the lung fluids, is the agent which stimulates abnormal collagen production in connective tissue are extremely tenuous. There is no positive evidence apart from the experiments of Kettle (25, 139) by subcutaneous injection of colloidal silicic acid, which must be regarded as doubtful because of the nature of his lesions; these were not growing nodules but contained areas of scar tissue repairing regions of necrosis produced by the toxic action of colloidal silicic acid; crystalline silica had a much smaller effect. Necrosis in the silicotic nodule does not precede fibrosis but is subsequent to it.

An apparent abundance of negative evidence is notably diminished when examined critically. On the one hand are the clinical reports of simple pneumoconiosis with absence of nodulation, diffuse x-ray shadowing or reticulation without discrete opacities, and long histories of exposure to siliceous dusts. These are cited as instances of the inhibition of solubility. It is imperative that accurate measurements of dust exposure and analyses of the dust should be available before a pronouncement be made in such cases. These data are invariably lacking, and it is suggested that most of the cases mentioned in this review can be accounted for in terms either of inert dust loading of the lungs or of diluted silica, with or without tuberculosis in each group.

On the other hand is the experimental work with animals. Evidence of the preventive action of a film of iron oxide upon silica particles seems to rest upon a single experiment by Kettle (25), using the method of subcutaneous injection. The effect of aluminium oxide films on solubility is definite, but King found that many low solubility dusts were pathogenic; he suggested that this might be a result of the film being dissolved away after the dust particles had deposited in the lungs (128).

The work of Gardner on carborundum dust (150) is usually quoted as supporting the solubility theory against the old idea of mechanical trauma by hard, sharp particles, a conclusion the author himself maintained; his paper describing the effects of inhaled dust of silicon carbide upon guinea pigs is worth quoting from. He is discussing the lungs of the control animals, which had inhaled dust, in comparison with others which had also inhaled tubercle bacilli of low virulence; the main mass of dust was scattered about the air spaces, and there was no fibrosis of the lung parenchyma:

> The tracheobronchial lymph nodes in both the dust controls and the injected series showed microscopic dust deposits at a somewhat later date than did the corresponding granite series; at two months an occasional particle was found, but it was not until the fourth month that any considerable quantity of dust had collected. From then on, until the sixteenth month, there was a steady increase in the deposits in both series. In the last five animals killed very large quantities were contained in all parts of the nodes. In the two dust controls of this period there was a very definite and somewhat extensive fibrosis which had obliterated the medullary sinuses. This reaction may be explained as the result of concentration of excessive amounts of irritant within a small focus.

Gardner also comments on the alteration of the course of the tuberculous process induced by the inhalation of a low virulent organism, from a self-limited process, usually healing by resolution, to a progressive tubercular bronchopneumonia.

Both the encouragement of tuberculosis and the initiation of fibrous growth in the lymph nodes, which are commonly accepted as specific attributes of silica (at least in experimental pneumonconiosis), are here described as the result of the presence of an inert dust.

The difficulty of carrying out inhalation experiments led to the use of intravenous and intratracheal injection. Gardner & Cummings (151), using the former technique, showed the importance of particle size. Particles of quartz between 6 and 12μ in size failed to produce silicotic nodules, while particles between 1 and 3μ did. The particles were transported by the blood stream to lungs, liver, and spleen; no reaction was observed in the kidneys. Necrosis and scar formation resembling that described by Kettle was produced at the site of injection in the ear.

The idea that a dust with a high specific surface was especially dangerous on account of its enhanced solubility was thus encouraged, but later experiments showed the existence of an optimum particle size for fibrosis in the region of 1 to 2μ (152, 153).

The great objection to the solubility theory of silicosis came with the discovery that the solubilities of various forms of silica did not always run parallel with their pathological effects (149, 154, 155). In the first place, it was established that samples of quartz from which an initial quantity of silicic acid could be leached readily did not thereby lose their fibrogenic effect, even though their subsequent solubility was very low. Secondly, four forms of silica, i.e., vitreous silica, quartz, cristobolite, and tridymite, have similar solubilities but produce differing fibrogenic effects, the intensities broadly increasing in the order named (156, 157).

The experiments of Kettle were conducted with colloidal solutions of silicic acid, and it is only recently that the physical chemistry of solutions of silica has been worked out sufficiently for their significance in the solubility theory of silicosis to be appreciated. Solutions of silicic acid may contain both monomeric and dimeric molecules and polymerised aggregates of sizes ranging up to the colloidal particles present in Kettle's solutions.

Molecularly dispersed solutions are excreted to a large extent after oral or intravenous administration without damage to the animal (158), and after oral administration of silica and silicates in man (159). Colloidal solutions, however, are toxic (158), precipitate protein (160), and produce scar type fibrosis, though not in the lung, from which they are too rapidly drained away (160). Policard & Collet (161) claim that the fibrosis is qualitatively similar to that produced by crystalline quartz, but quantitatively more prolific. There has thus been a tendency to accept the innocuous nature of molecular silicic acid and to associate the growth of silicotic nodules with colloidal solution.

The immediate objection to this view is that nothing remotely resembling a nodule has ever been produced by the administration of colloidal silica to animals, while human beings exposed to the dust of amorphous (not vitreous, which acts like crystalline) silica rarely develop disease unless the concentrations are abnormally high; in this case the clinical picture is quite different from silicosis (81 to 84).

These points are countered by arguing that inhaled dust of amorphous (i.e., dry, colloidal) silica is so soluble that its action in lung tissue is pro-

foundly modified, whereas classical silicosis could be attributable to the production of colloidal silicic acid *in situ* from particles of silica.

Doubt is thrown upon the last hypothesis by the failure to find amorphous silica in lung residues and by the fact that it is impossible to demonstrate the presence of colloidal silicic acid in extracts from crystalline or vitreous silica prepared under conditions which could hold in the lungs.

At high pressures and temperatures colloidal solutions are formed directly, but the quantity of silica dissolved has fallen to .02 per cent when the temperature is down to 200°C. (162). At body temperature solutions containing less than .016 per cent SiO_2 do not form a colloid; the transition from a true solution to a gel is slow in the vicinity of the above concentrations, and it is extremely unlikely that so high a figure is ever attained in tissue fluids (163).

Baumann (164) emphasised the complicated nature of solution equilibrium between crystal, colloid, and molecular phase, and the time taken to become stable; as a result, many determinations of alleged solubility were in reality measurements of rate of solution.

His figure for the solubility limit of molecular silicic acid was .012 to .014 per cent over the pH range 4.5 to 9.0, with a much higher value in more alkaline media. This figure was obtained for equilibrium between amorphous silica and solution, and it is interesting to note its closeness to the figures above for crystals at 200°C. (162) and gelling solutions prepared from sodium silicate (163).

Paterson & Wheatley (165) found the equilibrium concentration of molecular silicic acid to be .014 per cent irrespective of the presence of colloidal silica solution, but could not obtain any colloid in solutions made with crystalline silica.

A suggestive feature of these investigations is the recurrence of a figure around .014 per cent for equilibrium with both crystalline and colloidal material. It is certainly possible that the crystal surface is contaminated locally or generally with colloidal particles which are attached too strongly to float away into the solution yet provide a reservoir for maintaining the molecular equilibrium concentration.

As far as silicosis is concerned, the conclusion must be that any colloidal silica would have to be associated with the crystalline particles so closely as to necessitate their virtual contact with the fibre-forming cell in order to stimulate it. The actual amount of colloid could be extremely small.

Summary

Pneumoconiosis is the term used for a group of lung diseases caused by the accumulation of dust in the lungs without systemic effects immediately attributable to the dust. Some dusts are inert and produce neither an obvious reaction in the organ nor symptoms for diagnosis until a considerable quantity of dust has been collected. Free silica, usually in the form of quartz,

causes silicosis in which a continuous formation of collagen is stimulated in focal nodules which contain dust.

There are many reports of dusts containing quartz which have not caused silicosis; this is commonly put down to the inhibition of the fibrogenic action of quartz by other constituents of the dust which are known to decrease the solubility of quartz. Such reports, however, cannot be regarded as conclusive because there is seldom proof either of the inhalation by the victim of a sufficient concentration of quartz in particles fine enough to reach the lung alveoli, or of the presence of enough quartz in the lungs to cause the classical symptoms of silicosis. There is also a lack of parallelism in experimental silicosis between fibrogenic effect and solubility. On the other hand, there is some indication that the action of quartz in the lung is modified by the presence of a sufficient quantity of an inert diluent.

The production of developing fibrous growth in the lungs by inhaled dusts of crystalline or amorphous silicates is extremely doubtful. As naturally occurring, these dusts often contain free silica, and the presence of tuberculous infection may simulate silicosis. Fibrosis produced experimentally by these dusts is usually less than that produced by quartz and less focal. The experimental techniques are drastic and might be expected to produce such a reaction more readily than would be the case with long continued inhalation. Even inert dusts are suspected of encouraging the development of tuberculosis.

There are thus grounds for thinking that quartz and other forms of crystalline or vitreous silica are unique in causing proliferating fibrous nodules in connective tissue. The only other dusts which cause rapidly developing collagenous growth are fibrous silicates, loosely termed asbestos. The pathology of asbestosis contrasts with silicosis because the physical nature of the fibres renders them liable to become caught in the fine airways of the primary lobule. It is possible that chemical factors are concerned in the ensuing fibrosis which seems to lack the active progression of silicosis. Colloidal silicic acid is a tissue poison and has been suspected as the cause of silicosis, but the effects it produces lack characteristic features of the disease attributable to quartz dust, and it is doubtful if it can be formed by the solution of quartz in the lungs.

LITERATURE CITED

1. Ministry of Pensions and National Insurance, *Ann. Rept.* (1953)
2. Hugh-Jones, P., and Fletcher, C. M., *Med. Research Council Memo. No. 25.* (Her Majesty's Stationery Office, London, England, 1951)
3. Gloyne, S. R., *Lancet*, **I**, 810–14 (1951)
4. Fletcher, C. M., *Ber. med.-wiss. Arbeitstagung Silikose*, 119–150 (October, 1951)
5. Fletcher, C. M., *Arch. Ind. Health*, **11**, 29–41 (1955)
6. Cochrane, A. L., *Brit. J. Tuberc.*, **48**, 274–85 (1954)
7. Meister, P., *Arch. Gewerbepathol. Gewerbehyg.*, **14**, 214–26 (1956)
8. McLaughlin, A. I. G., Grout, J. L., Barrie, H. J., and Harding, H. E., *Lancet*, **I**, 337–41 (1945)
9. Keatinge, G. F., and Harding, H. E., *Brit. J. Ind. Med.*, **11**, 289–95 (1954)
10. Sander, O. A., *Arch. Ind. Hyg. and Occupational Med.*, **10**, 512–21 (1954)
11. Spencer, G. E., and Wycoff, W. C., *Arch. Ind. Hyg. and Occupational Med.*, **10**, 295–97 (1954)
12. Hamlin, L. F., *Ind. Med. and Surg.*, **21**, 1–4 (1952)
13. Symauski, H., *Arch. Gewerbepathol. Gewerbehyg.*, **13**, 702–20 (1955)
14. Pendergrass, E. P., and Leopold, S. S., *J. Am. Med. Assoc.*, **127**, 701–5 (1945)
15. Pendergrass, E. P., and Robert, A. G., *Radiology*, **50**, 736–45 (1948)
16. King, E. J., Macguire, B. A., and Nagelschmidt, G., *Brit. J. Ind. Med.*, **13**, 9–23 (1956)
17. Jötten, K. W., and Klosterkötter, W., *Arch. Hyg. u. Bakteriol.*, **139**, 314–24 (1955)
18. Ray, S. C., King, E. J., and Harrison, C. V., *Brit. J. Ind. Med.*, **8**, 62–67, 68–73 (1951)
19. Legerholtz, C., *Beitr. Silikose-Forsch.*, No. 56, 29–68 (1955)
20. Gloyne, S. R., Marshall, G., and Hoyle, C., *Thorax*, **4**, 31–38 (1949)
21. Harding, H. E., and Oliver, G. B., *Brit. J. Ind. Med.*, **6**, 91–99 (1949)
22. Dunner, L., and Bagnall, D. J. T., *Brit. J. Radiol.*, **22**, 573–79 (1949)
23. Parmeggiani, L., *Brit. J. Ind. Med.*, **7**, 42–45 (1950)
24. Sutherland, C. C., Fawcett, R., Crow, J., and Kemp, F. H., *Proc. Roy. Soc. Med.*, **38**, 519–34 (1945)
25. Kettle, E. H., *J. Pathol. Bacteriol.*, **35**(1), 395–495 (1932)
26. Heffernan, P., *J. Ind. Hyg. Toxicol.*, **8**, 481–90 (1926)
27. Caplan, A., and Burdon, D. J., *Proc. Inst. Mining Engrs. and Inst. Mining and Met. Conf.*, 33–67 (1947)
28. Ray, S. C., King, E. J., Harrison, C. V., and Mohanty, G. P., *Trans. Inst. Mining and Met.*, **61**, 343–49 (1952)
29. Thomas, R. W., *Lancet*, **I**, 133–35 (1952)
30. Bastenier, H., *Arch. belges. méd. sociale, hyg., méd. travail et méd. légale*, **8**, 81–84 (1950)
31. Chiappa, S., and Ferri, C., *Med. lavoro.*, **43**, 425–33 (1956)
32. King, E. J., Harrison, C. V., and Nagelschmidt, G., *J. Pathol. Bacteriol.*, **60**, 435–40 (1948)
33. Lynch, K. M., and McIver, F. A., *Am. J. Pathol.*, **30**, 1117–27 (1954)
34. Uytdenhoef, A., *Arch. belges méd. sociale, hyg., méd. travail et méd. légale.*, **13**, 219–70 (1955)
35. Deaner, S., *Lancet*, **II**, 417–20 (1941)
36. Tonning, H. O., *J. Ind. Hyg. Toxicol.*, **31**, 41–45 (1949)
37. Gattner, H., *Arch. Gewerbepathol. Gewerbehyg.*, **13**, 508–16 (1955)

38. McNally, D., and Tros
39. Rombola, G., and Gua
40. Peretti, L., and Occell
41. Occella, F., *Med. Lavo*
42. Sayers, R. R., Dallav
238 (Washington, I
43. Parmeggiani, L., *Rass*
44. Guilani, V., and Belli,
45. Russell, A. E., *Am. J*
46. Baetjer, A. M., *J. Ind*
47. Mohanty, G. P., Robe
G., *J. Pathol. Bacte*
48. Policard, A., and Coll
15, 343–50 (1954)
49. Klosterkötter, W., a
(1953)
50. Rotter, W., and Gärt
51. Russell, A. E., Britte
Health Bulletin No
52. Russell, A. E., *Public*
53. Moore, K. R., and K
54. Policard, A., Roche,
sociale, **8**, 165–75
55. Röhrl, W., *Arb. med.*
56. King, E. J., Ray, S.
Med., **7**, 37–41 (1
57. Landwehr, M., *Atla*
und nutzbaren M
Germany, 286 pp
58. King, E. J., Rogers,
G., *J. Pathol. Bac*
59. Jones, W. R., *J. Hyg*
60. Cooke, W. E., *J. Hy*
61. Gerstel, G., *Arch. Ge*
62. *Med. Research Coun*
London, England
63. Mavrogordato, A., J
64. Lemon, W. S., and
65. King, E. J., Gilchris
66. Landwehr, M., *Glüc*
67. Weiland, P., *Arch. C*
68. Hurlbut, S., and Be
69. Hass, H., *Zentr. Geu*
70. Dreessen, W. C., Da
and Trice, M. F
1940)
71. *Govt. India, Ministr*
72. Wade, T. W., *Mini*
Stationery Office

38. McNally, D., and Trostler, I. S., *J. Ind. Hyg. Toxicol.*, **23**, 118–26 (1941)
39. Rombola, G., and Guardascione, V., *Med. lavoro*, **46**, 480–97 (1955)
40. Peretti, L., and Occella, F., *Med. lavoro*, **45**, 700–14 (1954)
41. Occella, F., *Med. Lavoro*, **45**, 715–20, 721–29 (1954)
42. Sayers, R. R., Dallavalle, J. M., and Bloomfield, S. G., *Public Health Bull. No. 238* (Washington, D. C., 1937)
43. Parmeggiani, L., *Rass. med. ind.*, **20**, 400–9 (1951)
44. Guilani, V., and Belli, R., *Med. lavoro*, **46**, 715–24 (1955)
45. Russell, A. E., *Am. J. Med. Sci.*, **185**, 330–38 (1933)
46. Baetjer, A. M., *J. Ind. Hyg. Toxicol.*, **29**, 250–58 (1947)
47. Mohanty, G. P., Roberts, D. C., King, E. J., Harrison, C. V., and Nagelschmidt, G., *J. Pathol. Bacteriol.*, **65**, 501–12, (1953)
48. Policard, A., and Collet, A., *Arch. maladies profess. méd. travail et sécurité sociale*, **15**, 343–50 (1954)
49. Klosterkötter, W., and Jötten, K. W., *Arch. Hyg. u. Bakteriol.*, **137**, 625–36 (1953)
50. Rotter, W., and Gärtner, H., *Zentr. Arbeitsmed. u. Arbeitsschutz*, **4**, 35–40 (1954)
51. Russell, A. E., Britten, R. H., Thompson, L. R., and Bloomfield, J. J., *Public Health Bulletin No. 187* (Washington, D. C., 1929)
52. Russell, A. E., *Public Health Bulletin No. 269* (Washington, D. C., 1941)
53. Moore, K. R., and Kahlmann, C. G., *Med. J. Australia*, **II**, 267–74 (1939)
54. Policard, A., Roche, L., and Turc, *Arch. maladies profess. méd. travail et sécurité sociale*, **8**, 165–75 (1947)
55. Röhrl, W., *Arb. med. abhand. u. Berufskrankh. u. Verhütung*, No. 23 (1947)
56. King, E. J., Ray, S. C., Harrison, C. V., and Nagelschmidt, G., *Brit. J. Ind. Med.*, **7**, 37–41 (1950)
57. Landwehr, M., *Atlas zur Charakteristik der Silikosegefahrlichkeit von Gesteinen und nutzbaren Mineralien deutscher Lagerstätten*, (Bergbau-Berufs, Essen, Germany, 286 pp., 1947)
58. King, E. J., Rogers, N., Gilchrist, M., Goldschmidt, V. M., and Nagelschmidt, G., *J. Pathol. Bacteriol.*, **57**, 488–91 (1945)
59. Jones, W. R., *J. Hyg.*, **33**, 307–29 (1933)
60. Cooke, W. E., *J. Hyg.*, **35**, 207–18 (1935)
61. Gerstel, G., *Arch. Gewerbepathol. Gewerbehyg.*, **8**, 277–316 (1937)
62. *Med. Research Council (Brit.), 17th Ann. Rept.* (Her Majesty's Stationery Office, London, England, 1937)
63. Mavrogordato, A., *J. Chem. Met. Mining Soc. S. Africa*, **40**, 326–46 (1940)
64. Lemon, W. S., and Higgins, G. M., *Am. Rev. Tuberc.*, **32**, 243–56 (1935)
65. King, E. J., Gilchrist, M., and Rae, M. V., *J. Pathol. Bacteriol.*, **59**, 324–27 (1947)
66. Landwehr, M., *Glückauf*, 81–84, 117–86 (1948)
67. Weiland, P., *Arch. Gewerbepathol. Gewerbehyg.*, **8**, 412–25 (1937)
68. Hurlbut, S., and Beyer, D. S., *J. Ind. Hyg.*, **16**, 169–76 (1934)
69. Hass, H., *Zentr. Gewerbehyg. Unfallverhut.*, **24**, 193–201 (1937)
70. Dreessen, W. C., Dallavalle, J. M., Edwards, T. I., Sayers, M. R., Easom, H. F., and Trice, M. F., *U. S. Public Healtlh Bull. No. 250* (Washington, D. C., 1940)
71. *Govt. India, Ministry Labour, Rept. No. 3* (1953)
72. Wade, T. W., *Ministry Health, Welsh Board Health Rept. No. 38* (His Majesty's Stationery Office, London, England, 1927)

73. Tyrer, T. L., *Med. J. Australia*, **I**, 861–63 (1929)
74. Feil, A., *Méd. travail*, **7**, 56–59 (1935); *Bull. acad. méd.*, **113**, 105–9 (1935)
75. d'Onofrio, V., *Rass med. ind.*, **21**, 344–46 (1952)
76. Landwehr, M., and Bruckmann, E., *Beitr. Silikose-Forsch.*, No. 32, 132 (1955)
77. Middleton, E. L., *Lancet*, **II**, 1–9, 59–64 (1936)
78. Gärtner, H., and van Marwyck, C., *Deut. med. Wochschr.*, **72**, 708–10 (1947)
79. Gärtner, H., *Z. ges. inn. med. u. ihre Grenzgebiete*, **2**, 761 (1947)
80. Jötten, K. W., and Eikhoff, W., *Arch. Gewerbepathol. Gewerbehyg.*, **12**, 223–32 (1944)
81. Shaver, C. G., and Riddell, A. R., *J. Ind. Hyg. Toxicol.*, **29**, 145–57 (1947)
82. Jephcott, C. M., Johnston, J. H., and Finlay, G. R., *J. Ind. Hyg. Toxicol.*, **30**, 145–59 (1948)
83. Wyatt, J. R., and Riddell, A. R., *Amer. J. Pathol.*, **25**, 447–65 (1949)
84. *L.U. Gardner Memorial Volume*, 459–503 (Vorwald, A. J., Ed., Paul B. Hoeber, Inc., New York, N. Y., 659 pp., 1950)
85. King, E. J., Harrison, C. V., Mohanty, G. P., and Nagelschmidt, G., *J. Pathol. Bacteriol.*, **49**, 81–93 (1955)
86. Parada, A., *Med. y Seguridad del Trabajo*, **2**, 11–14 (1954)
87. Dreessen, W. G., and Dallavalle, J. M., *Public Health Repts. (U.S.)*, **50**, 131–43 (1935)
88. Dreessen, W. C., *J. Ind. Hyg.*, **15**, 66–78 (1933)
89. Hogue, W. L., and Mallette, F. S., *J. Ind. Hyg. Toxicol.*, **31**, 359–364 (1949)
90. Eason, H. F., Trice, M. F., and Carpenter, C. C., "A Study of the Effects of Mining and Milling of Pyrophyllite," *N. Carolina State Board Health* (1939)
91. Porro, F. W., Patton, J. R., and Hobbs, A. A., *Am. J. Roentgenol. Radium Therapy*, **17**, 507–524 (1942)
92. Siegal, W., Smith, A. R., and Greenburg, L., *Am. J. Roentgenol. Radium Therapy*, **49**, 11–29 (1943)
93. Greenburg, L., *Yale J. Biol. and Med.*, **19**, 481–501 (1947)
94. Reichmann, *V. Arch. Gewerbepathol. Gewerbehyg.*, **12**, 317–22 (1944)
95. Parmeggiani, L., *Rass. med. ind.*, **17**, 16–47 (1948)
96. Buus-Hansen, A., Frost, J., and Georg, J., *Ugeskrift Laeger*, **112**, 1691–97 (1950)
97. Köhler, G., Leopold, G., and Steyer, W., *Z. Ärztl. Fortbildung*, **45**, 375–82 (1951)
98. Friedman, P. S., Bell, M. A., and Solis-Cohen, L., *J. Am. Med. Assoc.*, **148**, 1418–19 (1952)
99. Hultgren, G. V., *Svenska Läkartidn.*, **48**, 540–42 (1951)
100. Millman, N. *Occupational Med.*, **4**, 391–94 (1947)
101. McLaughlin, A. I. G., Rogers, E., and Dunham, K. C., *Brit. J. Ind. Med.*, **6**, 184–94 (1949)
102. Alivisatos, G. P., Pontikakis, A. F., and Terzis, B., *Brit. J. Ind. Med.*, **12**, 43–49 (1955)
103. Miller, J. W., & Sayers, R. R., *Public Health Repts. (U.S.)*, **51**, 1677–88 (1936)
104. Policard, A. *Arch. maladies profess. méd. travail et sécurité sociale*, **2**, 530–39 (1939–40)
105. McLaughlin, A. I. G., *Arch. belges méd. sociale, hyg., méd. travail et méd. légale*, **8**, 451–60 (1950)
106. Mackay, W. A., and Gibson, J. B., *Brit. Med. J.*, **I**, 1077–78 (1948)
107. Smith, G. H., *Brit. Med. J.*, **I**, 1078–79 (1948)
108. Walker, W., *Brit. Med. J.*, **I**, 1079 (1948)

109. Baader, E. W., *Deut*
110. Merewether, E. R. *A*
111. Behrens, W., *Z. U*
112. Doll, R., *Brit. J. In*
113. *Annual Report of C* Office, London,
114. Kennaway, E. L., a
115. Kennaway, E. L., a
116. James, W. R. L., *B*
117. Gloyne, S. R., *Lan*
118. Rüttner, J. R., *Sch*
119. Policard, A., and C 16, 460–62 (195
120. Dewirtz, A. P., *Ar*
121. Ollivier, H., Mora *sécurité sociale,*
122. Alden, H. S., and
123. Speirs, R. S., and
124. Vorwald, A. J., D *tional Med.*, **3**,
125. King, E. J., Clegg,
126. Denny, J. J., Rob (1937)
127. Denny, J. J., Rob (1939)
128. King, E. J., *Med.*
129. Luton, P., Cham *sécurité sociale,*
130. Cartier, P., *Arch* (1949)
131. Noro, L., *Acta Pa*
132. Dreessen, W. C., R. R., *Public*
133. Dhers, V., Peller *travail et secur*
134. Erwin, J. R., *Ind*
135. Cirla, P., *Med. la*
136. Gardner, L. U., *A*
137. Belt, T. H., Ferr
138. Schuster, N. H.,
139. Kettle, E. H., *J.*
140. Miller, W. S., *Th*
141. Wasserman, F.,
142. Fitton Jackson,
143. Randall, J. T., *I*
144. Gardner, L. U.,
145. Gye, W. E., and (1924)
146. Gye, W. E., and

109. Baader, E. W., *Deut. med. wochschr.*, **75**, 50–51 (1950)
110. Merewether, E. R. A., *J. Ind. Hyg.*, **12**, 198–222, 239–57 (1930)
111. Behrens, W., *Z. Unfallmed. u. Berufskrankh.* **45**, 129–40, 179–89 (1952)
112. Doll, R., *Brit. J. Ind. Med.*, **12**, 81–86 (1955)
113. *Annual Report of Chief Inspector of Factories*, p. 79 (Her Majesty's Stationery Office, London, England, 127 pp., 1947)
114. Kennaway, E. L., and Kennaway, N. M., *Brit. J. Cancer*, **1**, 260–98 (1947)
115. Kennaway, E. L., and Kennaway, N. M., *Brit. J. Cancer*, **7**, 10 (1953)
116. James, W. R. L., *Brit. J. Ind. Med.*, **12**, 87–91 (1955)
117. Gloyne, S. R., *Lancet*, **I**, 1351–56 (1932)
118. Rüttner, J. R., *Schweiz. Z. allgem. Pathol. u. Bakteriol.*, **15**, 628–31 (1952)
119. Policard, A., and Collet, A., *Arch. maladies profess. méd. travail et sécurité sociale*, **16**, 460–62 (1955)
120. Dewirtz, A. P., *Arch. Dermatol. u. Syphilis*, **161**, 1–5 (1930)
121. Ollivier, H., Morand, P., and Brun, R., *Arch. maladies profess. méd travail et sécurité sociale*, **10**, 516–17 (1949)
122. Alden, H. S., and Howell, W. M., *Arch. Dermatol. u. Syphilis*, **49**, 312–14 (1944)
123. Speirs, R. S., and Wenck, U., *Proc. Soc. Exptl. Biol. Med.*, **88**, 89–93 (1955)
124. Vorwald, A. J., Durkan, T. M., and Pratt, P. C., *Arch. Ind. Hyg. and Occupational Med.*, **3**, 1–43 (1951)
125. King, E. J., Clegg, J. W., and Rae, V. M., *Thorax*, **1**, 188–97 (1946)
126. Denny, J. J., Robson, W. D., and Irwin, D. A., *Can. Med. Assoc. J.*, **37**, 1–11 (1937)
127. Denny, J. J., Robson, W. D., and Irwin, D. A., *Can. Med. Assoc. J.*, **40**, 213–28 (1939)
128. King, E. J., *Med. Research Council (Brit.), Spec. Rept. Ser. No. 250*, 69–94 (1945)
129. Luton, P., Champeix, J., and Faure, P., *Arch. maladies profess. méd. travail et sécurité sociale*, **12**, 629–33 (1951)
130. Cartier, P., *Arch. maladies profess. méd. travail et sécurité sociale*, **10**, 589–95 (1949)
131. Noro, L., *Acta Pathol. Microbiol. Scand.*, **23**, 53–59 (1946)
132. Dreessen, W. C., Dallavalle, J. M., Edwards, T. I., Miller, J. W., and Sayers, R. R., *Public Health Bull. No. 241* (Washington, D. C., 1938)
133. Dhers, V., Pellerat, J., Coudert, J., and Roche, L., *Arch. maladies profess. méd travail et securité sociale*, **7**, 19–23, 27–28 (1946)
134. Erwin, J. R., *Ind. Med.*, **16**, 439–41 (1947)
135. Cirla, P., *Med. lavoro*, **39**, 152–57 (1948)
136. Gardner, L. U., *Am. Rev. Tuberc.*, **45**, 762–66 (1942)
137. Belt, T. H., Ferris, A. A., and King, E. J., *J. Pathol. Bacteriol.*, **51**, 263–67 (1940)
138. Schuster, N. H., *J. Pathol. Bacteriol.*, **34**(ii), 751–57 (1931)
139. Kettle, E. H., *J. Ind. Hyg.*, **8**, 491–95 (1926)
140. Miller, W. S., *The Lung* (Charles C Thomas, Springfield, Ill., 222 pp., 1947)
141. Wasserman, F., *Anat. Record*, **111**, 145 (1951)
142. Fitton Jackson, S., *Proc. Roy. Soc. (London)*, [B] **142**, 536–48 (1954)
143. Randall, J. T., *Nature*, **174**, 853–55 (1954)
144. Gardner, L. U., *Am. J. Pathol.*, **13**, 13–14 (1937)
145. Gye, W. E., and Purdy, W. J., *Brit. J. Exptl. Pathol.*, **3**, 75–94 (1922); **5**, 238–50 (1924)
146. Gye, W. E., and Kettle, E. H., *Brit. J. Exptl. Pathol.*, **3**, 241–51 (1922)

147. Cummins, S. L., and Weatherall, C., *J. Hyg.*, **33**, 295–306 (1933)
148. Banting, F. G., *Can. Med. Assoc. J.*, **35**, 289–93 (1936)
149. King, E. J., *Occupational Med.*, **4**, 26–49 (1947)
150. Gardner, L. U., *Am. Rev. Tuberc.*, **7**, 344–57 (1923)
151. Gardner, L. U., and Cummings, D. E., *Amer. J. Pathol.*, **9**, 751–64 (1933)
152. King, E. J., Mohanty, G. P., Harrison, C. V., and Nagelschmidt, G., *Brit. J. Ind. Med.*, **10**, 76–92 (1953)
153. Zaidi, S. H., King, E. J., Harrison, C. V., and Nagelschmidt, G., *Arch. Ind. Health*, **13**, 122–32 (1956)
154. King, E. J., Zaidi, S. H., and Nagelschmidt, G., *Arch. Ind. Health*, **13**, 133–38 (1956)
155. Nagelschmidt, G., and King, E. J., *Staub*, **43**, 10–17 (1956)
156. Zaidi, S. H., King, E. J., Harrison, C. V., and Nagelschmidt, G., *Arch. Ind. Health*, **13**, 112–21 (1956)
157. Schmidt, K. G., and Luchtrath, H., *Beitr. Silikose-Forsch.*, No. 37, 1–43 (1955)
158. King, E. J., Stantial, H., and Dolan, M., *Biochem J. (London)*, **27**, 1007–14 (1933)
159. Whitehouse, A. G. R., *J. Ind. Hyg.*, **19**, 590–97 (1937)
160. Klosterkötter, W., *Arch. Hyg. u. Bakteriol.*, **138**, 522–32 (1954); **139**, 62–74 (1955)
161. Policard, A., and Collet, A., *Arch. Ind. Hyg. and Occupational Med.*, **9**, 389–95 (1954)
162. Frederickson, A. F., and Cox, J. E., *Am. Mineralogist*, **39**, 886–900 (1954)
163. Scheel, L. D., Fleischer, E., and Klemperer, F. W., *Arch. Ind. Hyg. and Occupational Med.*, **8**, 564–73 (1953)
164. Baumann, H., *Beitr. Silikose-Forsch.*, No. 37, 45–71 (1955)
165. Paterson, M. S., and Wheatley, K. H., *Safety in Mines Research Estab. Sheffield, Research Rept.*, No. 124 (1955)