fibrous tissue which ultimately forms the silicotic nodules.

Either due to the presence of the silica or to an inadequate blood supply the cells in the central portions of some of the nodules break down and disappear, leaving irregularly rounded collections of a very finely granular substance. This has the appearance of caseous necrotic material, and by microincineration is shown to contain a large amount of siliceous material.

SUMMARY

The cellular response to the injection of finely particulate silica begins very early, and there is a definite sequence of events, which takes place between the first appearance of abnormal cells (30 minutes) and the formation of firm, hyalinized, fibrous nodules (6 months). The type of reaction depends to a certain extent upon the amount of silica injected at one site.

There is a marked difference between the circumscribed necrotic mass resulting from the injection of a large amount of silica (which reacts as a foreign body) and the caseous, necrotic centres of the fibrotic nodules resulting from the disintegration of the dust-laden cells.

The phagocytosis of the quartz is not accomplished by the mononuclear leucocytes of the blood stream which first appear and are broken down in the aggregations, but by histiocytes which multiply in the surrounding tissue and migrate into the aggregations of silica particles.

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TISSUE REACTION TO SERICITE

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DURING the past two years considerable interest has been shown in the possible rôle played by sericite in the production of the fibrotic nodules characteristic of silicosis. Jones,[1] of England, has shown by petrological examination and chemical analysis that the mineral residues of the silicotic lungs of miners and the minerals from the mines producing injurious dusts contain considerable amounts of sericite. He implies that sericite is essential in the production of silicosis. It has also been contended that in certain mines (the Kolar Gold Fields, India), where the percentage of sericite in the ground rock is said to be exceedingly low, practically none of the miners develop silicosis, whereas in mines where the percentage of sericite in the ground rock is high silicosis frequently occurs. Much that has been written on this subject is of a speculative nature. Recent papers have discussed the plausibility of the sericite hypothesis, but few have advanced experimental evidence to prove or disprove it.

Because of the current interest in this subject we decided to investigate the reaction produced in various tissues by the injection of sericite in the purest form obtainable. The tissue reaction to this sericite has been compared with that produced by the element silicon, the oxide silica, a closely related silicate mica, and barium sulphate. Three samples of sericite obtained through the courtesy of Dr. Poitevin, of the Department of Mines, Ottawa, and another sample of sericite from the gold mines of northern Ontario were used. To facilitate comparison of the lesions produced all the experimental procedures were carried out in an identical manner, so that the conditions would be constant, except for the nature of the material injected. The tissues studied were lungs, subcutaneous tissue of the ears, peribronchial and pre-auricular lymphatic nodes of rabbits.

MATERIALS INJECTED

(1) *Sericite.*—Three samples of sericite received from Dr. Poitevin, of the Department of Mines, Ottawa, were from the following locali-

ties: (*a*) Wait-a-bit Creek, B.C.—This sericite is very pure. It was picked grain by grain and analyzed by Robert A. A. Johnston, of the Department of Mines, Ottawa. The results of this analysis are compared with those of Shannon[2] for sericite (quoted by Jones[1] in his paper) which they practically duplicate.

	Johnston	*Shannon*[2]
SiO_2	46.05	46.58
Al_2O_3	38.36	37.46
Fe_2O_3	0.97	0.80
CaO	2.04	Trace
MgO	0.47	1.16
K_2O	6.19	6.38
Na_2O	2.98	0.64
Li_2O	0.34	
Cs_2O	0.03	6.06 above 110° C.
H_2O	2.48	0.30 below 110° C.

(*b*) Saint John County, N.B.—This sericite is also about 99 per cent pure. No analysis is given. (*c*) Landing Cove, near Louisburg, N.S. —This sample may contain 5 to 6 per cent of free silica. (*d*) A sample of sericite containing an unknown amount of free silica, from one of the gold mines of northern Ontario.

(2) *Silicon.* (3) *Silica* (powdered quartz). (4) *Mica* (powdered white mica). (5) *Barium sulphate.*

PREPARATION OF MATERIALS

The materials prepared for injection into the ears were silicon, quartz, sericite from four different localities in Canada, mica, and barium sulphate. Each sample was crushed in a diamond mortar until the majority of the particles measured less than 5 μ in the greatest diameter. Two suspensions of each dust were made up in distilled water. Weighed amounts of dust were added so that one suspension contained 20, the other 50 mg. of dust per c.c. of water. The suspensions were then autoclaved for thirty minutes.

The materials used for intratracheal administration were the four samples of sericite and a sample of mica. They were prepared as described above, to give 50 mg. of dust per c.c. of distilled water. These suspensions were autoclaved for thirty minutes.

THE METHODS OF INJECTING MATERIAL

One c.c. of the "20 mg." suspension was injected subcutaneously into the right ear, and a similar amount of the "50 mg." suspension into the left ear of three rabbits, with a 10 c.c. syringe having a large bore needle.

The suspensions for intratracheal administration were introduced in 3 c.c. amounts through a number 18F hard fibre catheter which had been inserted to the bifurcation of the trachea and then withdrawn a distance of one cm. The suspension was delivered into the catheter by means of a syringe. The material remaining in the catheter was forced into the bronchi with 2 or 3 c.c. of air. Three rabbits were used for each sample of dust.

OBTAINING MATERIAL FOR STUDY

At time-intervals of 4, 5 and 6 months one of each group of rabbits of the subcutaneously injected series was killed. The portions of the ears containing the injected materials and the pre-auricular lymphatic nodes were taken for study.

Four, five and six months after the intratracheal injections of the dusts one rabbit of each group was killed, and the lungs and mediastinal lymphatic nodes were taken for section.

The tissues were fixed in formalin, dehydrated in alcohol, embedded and cut in paraffin. The siliceous material was demonstrated in adjoining sections by the technique of microincineration[3] and subsequent treatment of the ash with concentrated hydrochloric acid.

MICROSCOPIC EXAMINATION OF TISSUES

EARS

1. SERICITE. — (*a*) *British Columbia sericite* — 6 months.

Sections of rabbit ear show large numbers of endothelial giant-cells containing sericite on one side of the ear cartilage. The giant-cells are of the foreign body type, each having a large number of granular vesicular nuclei, with one prominent nucleolus, arranged around the periphery of the cell. The nuclei are deeply stained and prominent. There is no evidence of degeneration of these cells. The sericite is in the form of fine fibres and scales. It is pale green in colour, and is seen in the central portions of the giant-cells. The particles have retained their sharply defined outlines and are still doubly refractive. Large groups of giant-cells are surrounded by strands of acellular, hyalinized connective tissue. There is no evidence of fibrosis.

The reactions produced in the ears by the injection of sericite from New Brunswick (Fig. 3), Nova Scotia, and Ontario are so similar to those produced by British Columbia sericite that a detailed description would merely be a repetition of the microscopic picture described above.

2. SILICON DIOXIDE—6 months.

Sections of rabbit ears show a number of rounded fibrotic nodules in the subcutaneous tissue on one side of the ear cartilage. The nodules are composed of elongated, spindle-shaped fibroblasts, arranged concentrically to form large whorls. Some of the whorls are confluent, others are separated by wide strands of hyalinized acellular connective tissue. This dense connective tissue also surrounds the whole group of nodules. Only the larger particles of quartz are visible and doubly refractive. The intracellular siliceous material is not doubly refractive.

3. SILICON—6 months.

Sections of rabbit ears show many large and small aggregations of fine particles of silicon in the tissue spaces of the subcutaneous tissue on one side of the ear cartilage. The silicon is black. It is not doubly refractive. It is seen as irregularly rounded and elongated aggregations of fine particles lying free in the tissue spaces of fairly dense hyalinized connective tissue of the ear. The fine black particles are also seen in the cytoplasm of an occasional tissue histiocyte. There is no evidence of any cellular reaction to this material. (Fig. 6).

4. BARIUM SULPHATE—6 months.

Sections of rabbit ear show numerous large endothelial giant-cells, each containing a large amount of barium sulphate distributed diffusely throughout the subcutaneous tissue on one side of the ear cartilage. The giant-cells are of the foreign-body type, with many granular vesicular nuclei (each with one prominent nucleolus) congregated in crescent formation at one end of the cell. These cells all contain a large amount of barium sulphate which has a uniform finely granular appearance and is greyish brown in colour. This material is not doubly refractive. Single giant-cells or small groups of these cells are surrounded by thin strands of hyalinized acellular connective tissue. The barium sulphate is also seen in an occasional distended histiocyte at a distance from the main mass. (Fig. 4).

LUNGS

1. SERICITE. — (*a*) *British Columbia sericite* — 6 months.

Sections of rabbit lung show numbers of alveolar spaces, in small and large irregular foci in the parenchyma of the lung, filled with endothelial giant-cells containing sericite. The giant-cells are of the foreign body type, having numerous granular vesicular nuclei, with one prominent nucleolus congregated towards one end of the cell, usually in crescentic formation. The clear cytoplasm of the cells contains varying amounts of sericite in the form of fine fibres and scales. The nuclei are prominent and stain deeply. The cells do not appear

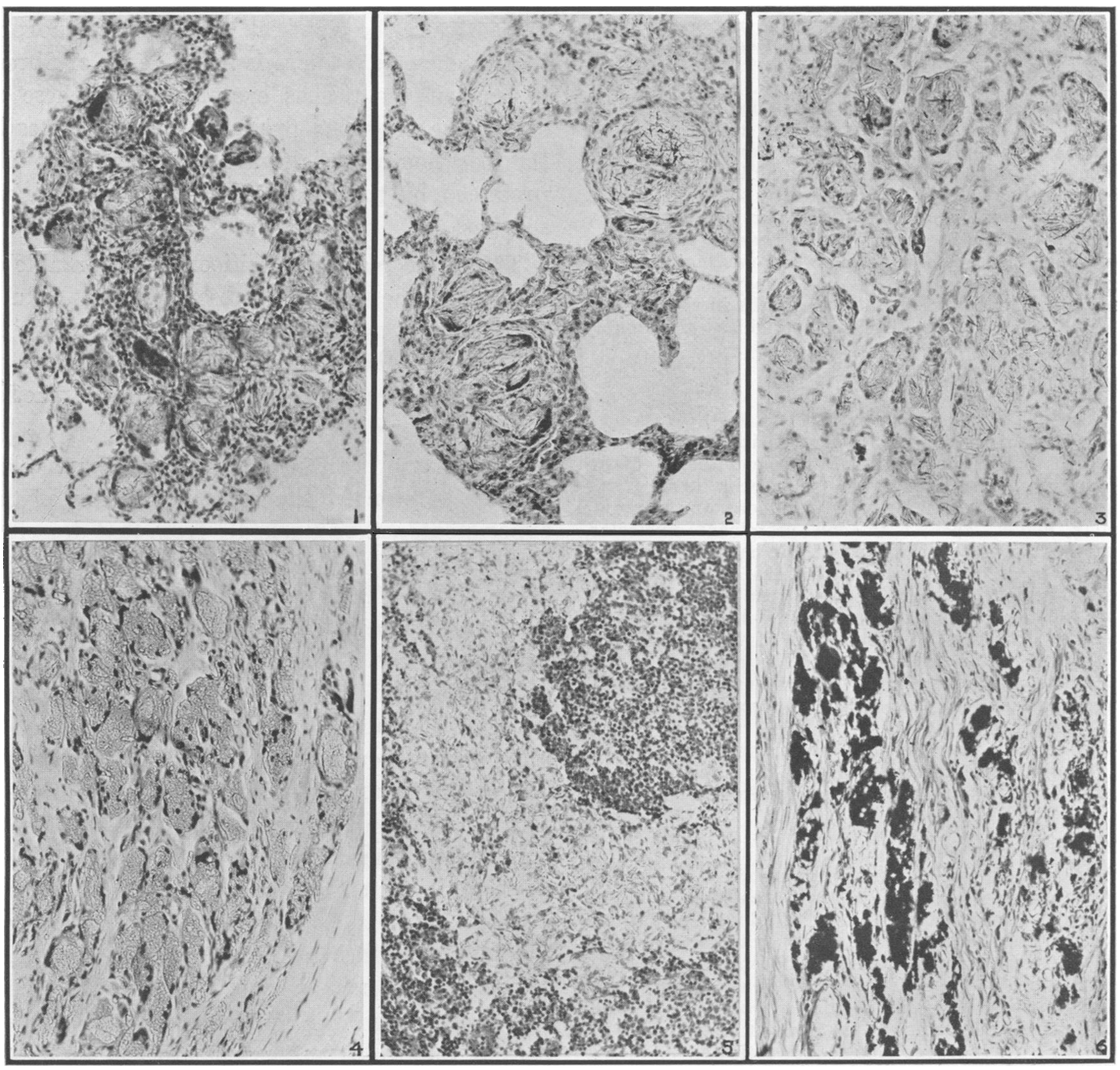

FIG. 1.—Lung, sericite, New Brunswick—6 months. FIG. 2.—Lung, sericite, British Columbia—6 months. FIG. 3.—Subcutaneous tissue, sericite, New Brunswick —6 months. FIG. 4.—Subcutaneous tissue, barium sulphate—6 months. FIG. 5.—Lymph node, sericite, New Brunswick—6 months. FIG. 6.—Subcutaneous tissue, silicon—6 months.

to be damaged in any way by the presence of the sericite. The fibres and scales of sericite retain their sharply defined outlines and their bi-refringence. Some of the giant-cells are small and lie free in the alveolar spaces; others are so large that they fill the spaces, frequently distending them. When the giant-cells fill the spaces they are usually surrounded by two or four layers of alveolar endothelium. The surrounding alveolar spaces and the remainder of the lung tissue are not remarkable. There is no evidence of fibrosis or fibrotic nodule formation. (Fig. 2).

The cellular reaction to New Brunswick (Fig. 1) and Nova Scotia sericite in the lung tissue, as in the ears, is so similar to that produced by British Columbia sericite that no distinction can be made microscopically.

2. MICA

Sections of rabbit lung show a number of groups of adjacent alveolar spaces filled with fine scales of mica. The alveolar walls are still intact and appear as septa traversing the aggregations of mica particles. A few foreign body giant-cells containing mica particles are seen in alveolar spaces. These cells do not appear to be damaged in any way by the presence of the mica. In most of the affected alveoli the particles are lying free in the spaces. There is no evidence of fibrosis. The remainder of the lung tissue is not remarkable. The mica particles are doubly refractive.

3. SILICA—6 months.

Sections of rabbit lung show numerous fibrotic nodules. The nodules are irregularly rounded in outline and vary considerably in size. Some of them are confluent; others are discrete. The nodules are composed of fibroblasts arranged concentrically to form whorls. The central portions of many of them have a caseous necrotic appearance. Each nodule has a number of thin-walled blood-vessels. The surrounding alveolar spaces contain many dust-filled monocytes. There is extensive thickening of the alveolar walls in the affected foci. Only the large particles of silica are doubly refractive.

LYMPHATIC NODES

1. SERICITE.—*British Columbia*—6 months.

Sections of pre-auricular lymphatic nodes show a number of lymph sinuses filled with endothelial giant-cells containing sericite. The giant-cells are of the foreign-body type, having a number of granular vesicular nuclei, each with one prominent nucleolus, arranged around the periphery of the cells. The giant-cells contain in their central portions fine fibres and scales of sericite, which is pale green in colour. A number of the lymphatic sinuses are filled with these giant-cells. There is no destruction of the architecture of the lymphoid or reticulo-endothelial elements of the gland. There is no evidence of fibrosis in or around the aggregations of giant-cells. The smallest particles retain their bi-refringence.

The cellular reaction to New Brunswick (Fig. 5), Nova Scotia, and Ontario sericites in the lymphatic nodes is similar to that produced by British Columbia sericite.

2. SILICA.—6 months.

Sections of pre-auricular lymphatic nodes show fairly extensive destruction of the architecture of the node by the formation of fibrotic nodules. The fibrotic nodules have caseous necrotic, finely granular, acellular central portions, surrounded by fibroblasts arranged concentrically to form whorls. The whorls are surrounded by thick layers of hyalinized connective tissue. The fibrous nodules appear to form in the lymphatic sinuses and extend, replacing the reticulo-endothelial elements and destroying the lymphoid elements of the lymphatic node. Numerous fibrotic nodules are seen at the sites of the peripheral lymphatic sinuses which are almost completely fibrosed. Only the larger particles of quartz are doubly refractive.

COMMENT

The tissue reaction to the injection of sericite is essentially the same in the different tissues studied. The reactions produced by samples of sericite from four widely separated districts are so similar that they cannot be distinguished microscopically. The reaction closely resembles that produced by an innocuous foreign body. The particles of sericite are taken up by foreign body giant-cells, which either remain at the site of injection or transport the material to the sinuses of the regional lymphatic nodes. Only the finer particles of sericite are seen in the lymphatic nodes. There is no difference in the severity or extent of the reaction in the tissue sections taken at 4, 5 and 6 months after injection. The fine particles of sericite remain doubly refractive in the giant-cells and show no morphological changes. There is no evidence of fibrosis in any of the tissues examined. In these respects the reactions produced in the tissues by the injection of sericite are very similar to that produced by the injection of mica and barium sulphate.

The tissue reaction to silicon is remarkable on account of the noticeable absence of any cellular proliferation. The material appears to lie innocently in the tissue spaces. The tissue response to silicon closely resembles the reaction to the presence of carbon particles.

The tissue reaction to finely particulate quartz, as seen in the control animals of this experiment, differs markedly from that described above. It has been described in detail in another paper of this series, "The Cellular Reaction to Silica".[4] In these tissues definite nodular fibrosis is seen in the lungs, subcutaneous tissues and lymphatic nodes in the sections taken at 4, 5 and 6 months. They show a definite progression in the pathological changes taking place, until typical fibrotic nodules are formed. In the later stages many of the fibrotic nodules produced by the injection of finely particulate quartz have caseous necrotic central portions. On the other hand we have not observed any necrotic areas in the lesions produced by sericite, no matter how extensive the giant-cell reaction to the injection or how closely packed these cells might be. In the lung, following quartz injection, large groups of alveoli are destroyed and replaced by fibrotic nodules. When sericite is injected in the same manner groups of alveoli become filled with giant-cells containing the dust, but there is no destruction of lung tissue.

It is interesting to note that the Nova Scotia and Ontario sericites containing some free silica produce no fibrous tissue reaction. Even the small particles of sericite retain their original size and sharp, clearly cut outline throughout the period of observation and are still doubly refractive. The smaller silica particles soon lose their bi-refringence.

When the materials are injected subcutaneously our findings in the subcutaneous tissues and regional lymphatic nodes are in agreement with those of Kettle.[5] The results of intratracheal injection are also very similar to those of Lemon and Higgins,[6, 7] who were unable to produce fibrotic nodules by introducing aluminium oxide and borosilicate-glass intratracheally, but produced definite nodules by the introduction of silica in this manner.

SUMMARY

Sericite was introduced in watery suspension into the lungs of rabbits. Similar suspensions were injected subcutaneously into the ears. The cellular reaction in the tissues and regional lymphatic nodes was followed at intervals and compared with that of finely particulate silicon, silica, mica and barium sulphate. The reaction to sericite is comparable to that produced by the innocuous substances, but not to that to free silica. Various samples of sericite from Nova Scotia, New Brunswick, British Columbia and Ontario were used in these experiments.

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THE TREATMENT OF CANCER OF THE LARYNX AND HYPOPHARYNX*

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IT is stated that in Canada each year 10,646 persons die from cancer. In recent years renewed interest has been shown in the treatment of cancer, and particularly of cancer of the larynx and hypopharynx. Since the pioneer work of Semon[1] and Butlin[2] much has been added to our knowledge. The surgical mortality has been markedly decreased by improvement in technique. The reported success of StClair Thomson,[3] Colledge[4] and Trotter[5] in England, of Gluck in Germany, Tapia in Spain, and MacKenty, Jackson and others in the United States has stimulated all laryngologists to greater effort. The percentage of cures today of cancer of the larynx is probably greater than in that of any other part of the body. To quote Crile—"There is no surgical operation that offers so certain and so permanent a cure for cancer as total laryngectomy in intrinsic cancer of the larynx."

Early diagnosis has been stressed as the *sine qua non* in the successful treatment of cancer. This is particularly so in regard to the larynx and hypopharynx. It is a tragic fact that, in spite of the extensive educational propaganda of the press, both medical and lay, and in spite of the many addresses on the subject, relatively few cases are referred to the laryngologist in the early stage.

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