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Experimental study of the tissue reactions to certain dusts with the object of predicting their clinical activity

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AN EXPERIMENTAL STUDY OF THE TISSUE REACTIONS TO CERTAIN DUSTS WITH THE OBJECT OF PREDICTING THEIR CLINICAL ACTIVITY.

by

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TABLE OF CONTENTS

INTRODUCTION

In the past few decades, due to man's greater contact with fumes and dusts, a great interest in the effects of inhalation of these substances has arisen. The various industries in which man now engages has caused contact with dusts and fumes which have acted deleteriously upon the human organism. Of recent years there has been considerable legislation governing the proper ventilation and working conditions where various toxic substances are found in the atmospheres which men breathe. The work on the pneumoconioses has been prolific. Considerable amounts of data based on clinical and experimental observations have accumulated. This data has segregated certain dusts which have been proved both clinically and experimentally to be harmful. Certain other dusts have been found to exert no harmful effects from inhalation. It is the purpose of this thesis to present studies on the tissue reactions produced by certain dusts which dusts have never before been studied from the view point of their possible harmfulness on inhalation.

HISTORICAL

Collis 1915 (1) gives an excellent review of the very early observations in regard to the effects of dust on man. He states that Hippocrates and Pliny the Elder both mention dust and its relation to disease, but it was not until 1557 that Georgius Agricola gave a definite description of the possible harmful

effects of dust inhalation. Agricola advocated ventilation of mines and wrote concerning them: "The mines are very dry and constant dust enters the blood and lungs, producing the difficulty breathing that the Greeks call asthma. When the dust is corrosive it ulcerates the lungs and produces consumption, hence it is that in the Carpathian mountains there are many women who have married seven husbands, all of whom this dreadful disease has brought to an early grave." Lohneiss suggested the relation of dust inhalation to tuberculosis in 1670. He wrote: "The dust and stones fall upon the lungs, the men have lung disease, breathe with difficulty, and at last take consumption." Ramazzini of Padua in 1705 described autopsies on the lungs of stone cutters in whose lungs he found, "...heaps of sand that in running the knife through the pulmonary vesicles he thought that he was cutting some sandy body." Thomas Benson in 1713 patented a method for the wet pounding of flints because when flints are pounded dry, "...the process proved very destructive to mankind insomuch that any person, ever so healthful and strong, working in that business cannot possibly survive over two years, occasioned by the dust sucked into his body from the air he breaths."

With the discovery of the tubercle bacillus by Koch in 1882 the relationship of this organism to the disease produced by the inhalation of certain dusts was soon pointed out. Haldane 1904 (2) investigated the causation of the high phthisis rate among

Cornish tin miners. He decided that, "So far as the Cornish miners are concerned it seems evident enough that stone dust which they inhale produces permanent injury of the lungs....and that this injury while it is apparently capable of gradually producing by itself impairment of the respiratory functions and indirectly of the general health, also predisposes enormously to tuberculosis of the lungs, so that a large proportion of miners die from tuberculosis. That the primary injury to the lungs is due solely to inhalation of stone dust would seem to be practically certain."

Collis 1915 (3) showed in a statistical analysis that respiratory diseases such as tuberculosis, bronchitis, pneumonia, and asthma were far more common among those workers exposed to dusty atmospheres than others not exposed. He writes that clinical observation has shown that inhalation of coal or cement does not cause lung disease or entail disablement. In so doing he made the earliest differentiation between harmful and non-harmful dusts.

In an attempt to show the relationship of silica and tuberculous infection Gye and Kettle 1922 (4) performed a simple yet an ingenious experiment. Into one flank of a mouse they injected silica, into the other flank carbon. Tubercle bacilli were injected into both lesions. In the silica nodules the bacilli proliferated in the coagulum, but in the carbon nodule there was no proliferation of the bacilli. Kettle 1932 (5) expanded this experiment and

using o.1 to o.2 gm. injections of various dusts subcutaneously in mice and rabbits showed that dusts could be divided on their reaction subcutaneously into those which are proliferative and those which are inert. The various dusts used were silica, mine dust, shale, kaolin, asbestos, carborundum, iron oxide, carbon, coal, marble, aluminum oxide, magnesium oxide, and calcium oxide. Several days after the dusts were injected a culture of tubercle bacilli was injected into the various animals. It was found that the proliferative dusts (silica containing) showed intense tuberculous reaction with many bacilli in the nodules. The inert dusts (coal, carbon, iron oxide, etc.) showed no tuberculous reaction in the dust nodules. He states that these findings agree with clinical observations.

Why the tubercle bacillus shows an affinity for silicotic nodules has not been definitely determined. Kettle 1924 (6) states that silica has some specific action on the growth of tubercle bacilli in the tissues. This action may be due to the mechanical protection of the bacilli by the coagulum from the defensive mechanisms of the body, it may be due to the rich pabulum furnished by disintegrated cells, or it may be due to some stimulating action of silica on the growth of the bacilli alone.

It is out of the possibility of dust inhalation predisposing to tuberculosis and other respiratory diseases that the great interest in the pneumoconioses has arisen.

MATERIALS AND METHODS

Various methods for the study of the action of dusts on tissues as an index of their clinical activity have been used in the past. The technique of administration of dusts to experimental animals which is most like actual conditions of exposure of man is of course the actual inhalation of air from an atmosphere containing the dust under investigation. In 1924 Carleton (7), an English worker, first used the inhalation of dusts by guinea pigs on a large scale to study the harmfulness of certain dusts. Haynes 1931 (8) credits arnold in 1885 for having first experimentally dusted laboratory animals. Haynes himself exposed guinea pigs to the inhalationof various dusts. The classic work on experimental inhalation of dusts by laboratory animals was not done however until Gardner 1932 (9) published his remarkable study on the inhalation of quartz dust by guinea pigs. His work is the first really scientific experimental approach to the question of the effects of dust on the tissues. In his experiments the particle size, and number of particles per cubic foot were determined as the dust exposures went along. He explains the mechanism of silicosis production in the lung and emphasises the length of time required for its production experimentally. He exposed his animals 8 hours per day 6 days a week for a year or more.

Kettle 1930 (10) and Kettle and Hilton 1932 (11) introduced the method of intratracheal insufflation of dusts into laboratory

animals as a method for the experimental study of the effects of dusts on tissues. They used a suspension of sterile dust in sterile physiological saline. One to 2cc. of a 3-4% suspension was used. They report favorable results with the technique.

Gye and Kettle 1922 (4), Kettle (5), and Kettle (6) describe the subcutaneous injection of dusts. They used 0.1 to 0.2 gm. of dust in 1 to 2 cc. of sterile saline as the dosage. They report favorable results with this technique also.

One of the most recent techniques of administration of dust to animals so as to study tissue reactions is the intraperitoneal method introduced by Miller and Sayers 1934 (12). They published similar studies on this method in 1934 (13), 1935 (14), 1935 (15), and 1936 (16). The dosage of dust used by them was 0.2 gm. of dust in 2 cc. of sterile saline. Particle sizes of the dusts varied from 0.75 to 1.7 microns. The animals were killed at various times up to and including one year. McCord, Fleming, Ainslee, and Johnson 1936 (17), and McCord, Kasper, and Brosius 1937 (18) used the same technique of administration in their studies of certain dusts.

Gardner 1933 (19) advanced another technique, that of intravenous administration of the dust. He watched the reaction to the dust in the liver, spleen, and lungs, when administered in this manner.

The techniques used in the present study were actual inhalation of the dust by guinea pigs, intratracheal insufflation, and sub-

cutaneous injection in rabbits, and intraperitoneal injection into rats.

In all sixteen various dusts were studied in this experiment. Several dusts whose actions, clinically and experimentally, have long been known, were used as controls, while several other dusts about whose actions nothing is known were also studied. The control dusts were silica (quartz), bituminous coal, jeweler's rouge (hematite or ferric oxide), and talc. The unknown dusts were for the most part the decomposition products of projection arc carbon electrodes and various substances used in the making of electrodes. The various samples were: "suprex" electrode mixture, "suprex" #5643, "suprex" #x-2, "suprex" #5913, "suprex" #5915, "suprex" #5914, therapeutic electrode dust #5967, electrode carbon, electrode core material (for the most part rare earth substances), calcium phosphate, copper oxide, and calcium fluoride.

Particle size of these various dusts was determined by preparing a film of dust on a microscopic slide according to the technique of Green 1921 (20). This film was examined and the sizes of 200 particles determined by a Bausch and Lomb ocular micrometer which can measure accurately to as small a particle as 0.75 microns.

The chemical composition, particulate composition, and photomicrograph of the various dusts studied are presented on the following pages.

SILICA: (quartz)

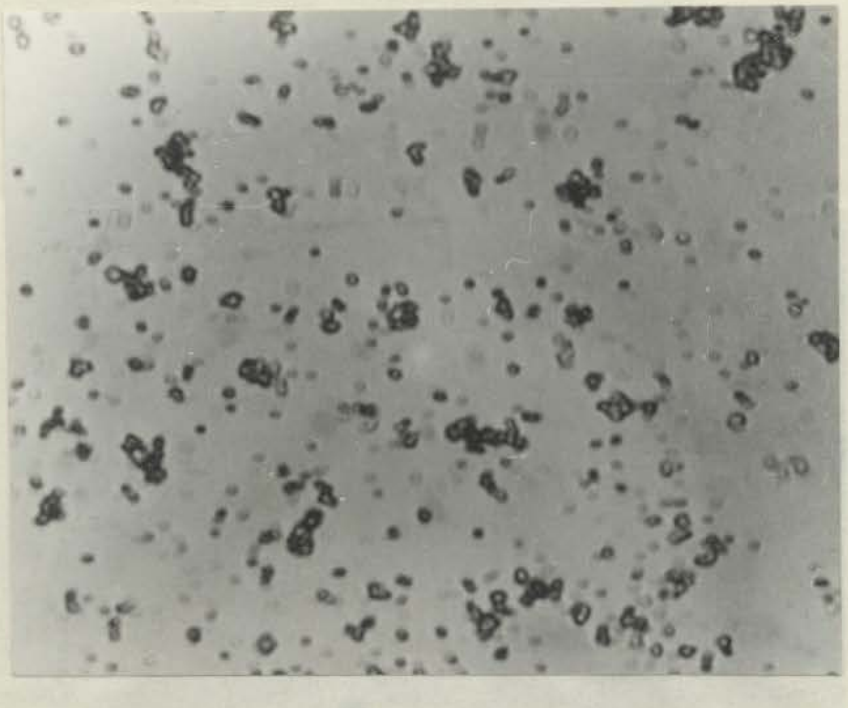
Chemical Composition:

SiO_2 So called "free silica".

Particle Size:

0.75 to 1.5 microns	92%
3 microns	5%
4.5 microns	2%
6 microns	1%

PHOTOMICROGRAPH OF SILICA: 440x



BITUMINOUS COAL:

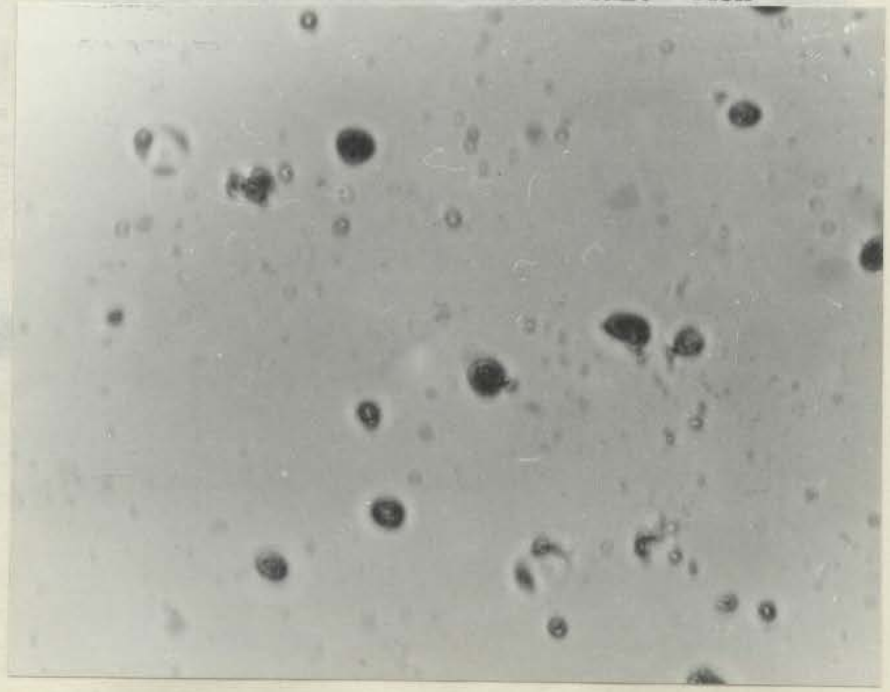
Chemical Composition: (21)

Carbon	55%
Hydrogen	5.5%
Nitrogen	1.0%
Oxygen	20%
Sulphur	4.0%
Ash	8.0%
Silica	o.8 to 3.5%

Particle Size:

o.75 to 1.5 microns	59%
3 microns	24%
4.5 microns	9%
6 microns	6%
7.5 microns	2%

PHOTOMICROGRAPH OF BITUMINOUS COAL: 440x



JEWELER'S ROUGE: (Hematite)

Chemical Composition: (22)

Fe_2O_3 ..... 56% and above

Silica ..... 5% and less

Particle Size:

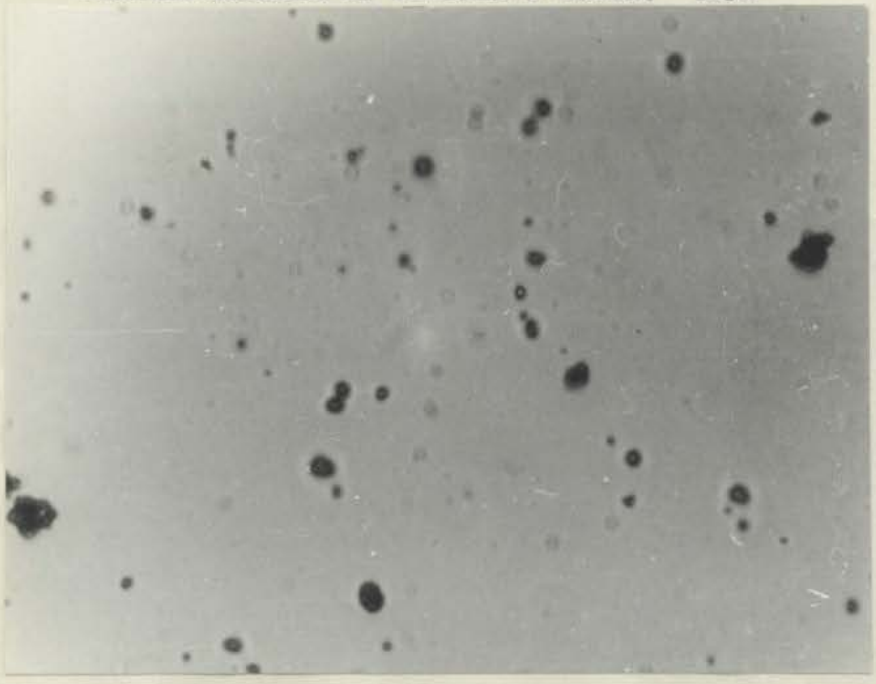
0.75 to 1.5 microns 91%

3 microns 7%

4.5 microns 1%

6 microns 1%

PHOTOMICROGRAPH OF JEWELER'S ROUGE: 440x



TALC: (Hydrous magnesium silicate)

Chemical Composition: (23)

Talc .. $H_4(MgFe)_3Si_2O_9$ ...	82.7%
Calcium carbonate	8.7%
Magnesium carbonate	7.6%

Particle Size:

0.75 to 1.5	80%
3 microns ...	12%
4.5 microns .	5%
6 microns ...	3%

CARBON:

Chemical Composition:

Commercially pure carbon.

Particle Size:

0.75 to 1.5 microns	78%
3 microns	10%
4.5 microns	2%
6 microns	1%
7.5 microns	1%

ELECTRODE CORE MATERIAL: (24)

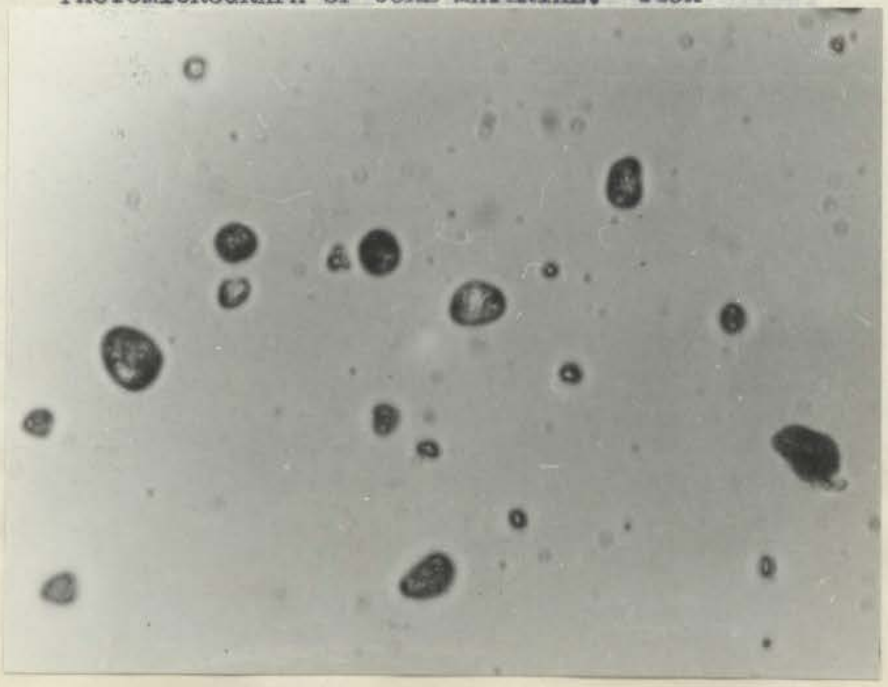
Chemical Composition:

Cerium oxide	46%
Lanthanum oxide	22%
Neodymium oxide	22%
Praseodymium oxide	8%
Samarium oxide	3%

Particle Size:

0.75 to 1.5 microns	50%
3 microns	25%
4.5 microns	9%
6 microns	7%
7.5 microns	5%
9 microns	4%

PHOTOMICROGRAPH OF CORE MATERIAL: 440x



"SUPREX" ARC ELECTRODE DUST: (24)

Chemical Composition:

	Sample #1	Sample #2
Silicon dioxide	1.79%	1.21%
Rare Earth oxides ...	65.70%	71.80%
Ferric oxide	2.26%	1.46%
Calcium oxide	.53%	.20%
Potassium oxide	2.26%	2.38%
Sulphur trioxide	2.35%	2.98%
Phosphorous pentoxide .	.17%	.15%
Fluoride	10.65%	11.31%
Boric anhydride	.50%	.60%

All samples contained a small amount of copper. A suspension of #1 in distilled HOH showed a pH of 5.5. All samples contained some unburned carbon and #2 a small amount of manganese. The Rare earth substances are for the most part combined with the fluoride, the compounds being extremely insoluble in water. The calcium is probably as the sulphate. For chemical composition of Rare Earth oxides see analysis of core material.

Particle Size:

See individual dust samples which follow.

"SUPREX" MIXTURE:

Chemical Composition:

The same as that given on p. 13.

Particle Size:

0.75 to 1.5 microns	82%
3 microns	10%
4.5 microns	4%
6 microns	2%
7.5 microns	1%
9 microns	1%

"SUPREX" #5913

Chemical Composition:

The same as that given on p. 13 except no copper present.

Particle Size:

0.75 to 1.5 microns	82%
3 microns	11%
4.5 microns	5%
6 microns	2%
7.5 microns	2%

"SUPREX" #5915

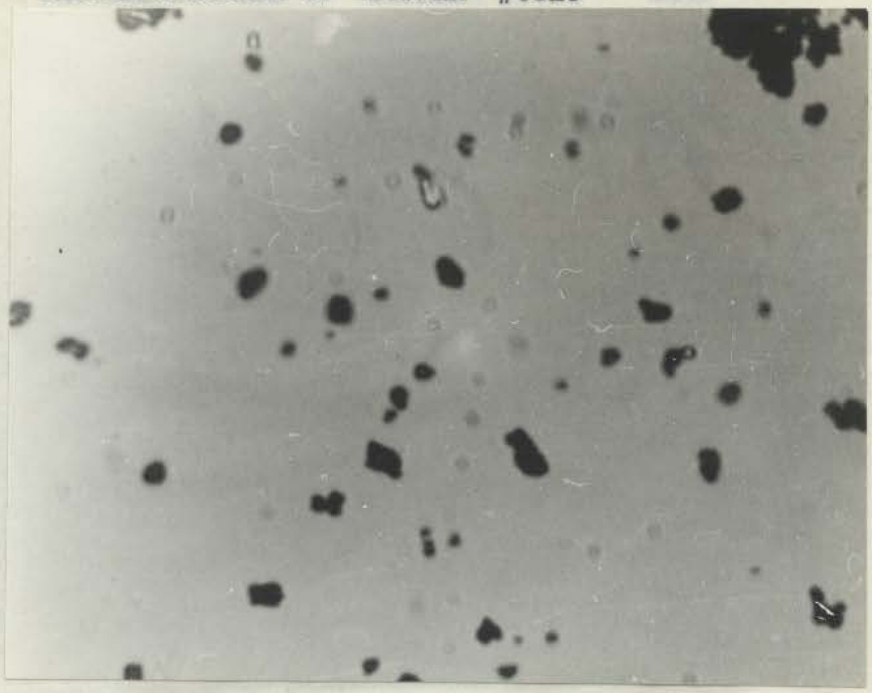
Chemical Composition:

The same as that given on p. 13.

Particle Size:

0.75 to 1.5 microns	83%
3 microns	9%
4.5 microns	5%
6 microns	2%
7.5 microns	1%

PHOTOMICROGRAPH OF "SUPREX" #5915



"SUPREX" #5643

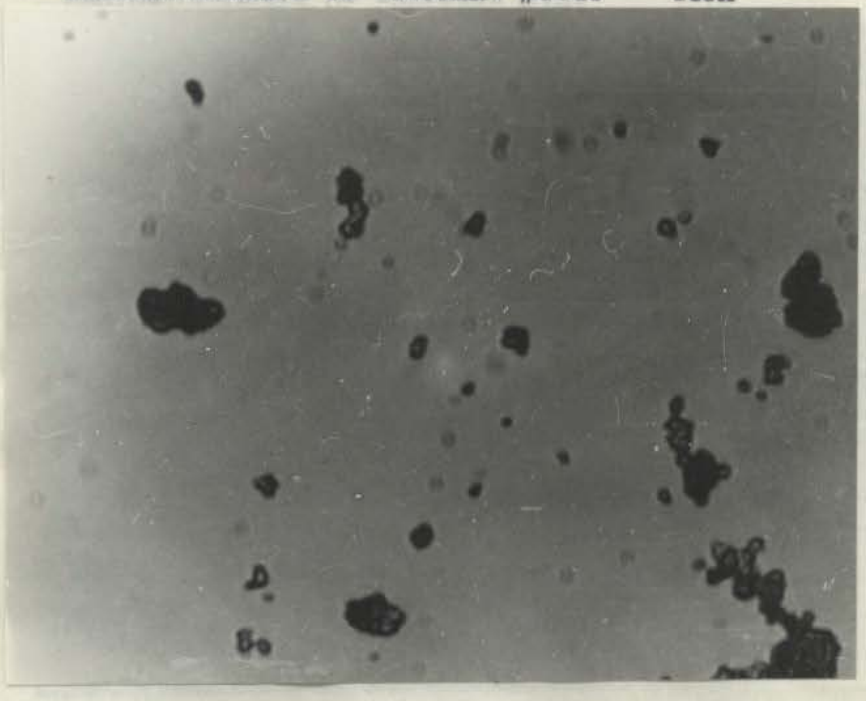
Chemical Composition:

The same as that given on p. 13.

Particle Size:

0.75 to 1.5 microns	78%
3 microns	12%
4.5 microns	5%
6 microns	4%
7.5 microns	1%

PHOTOMICROGRAPH OF "SUPREX" #5643 440x



"SUPREX" #x-2

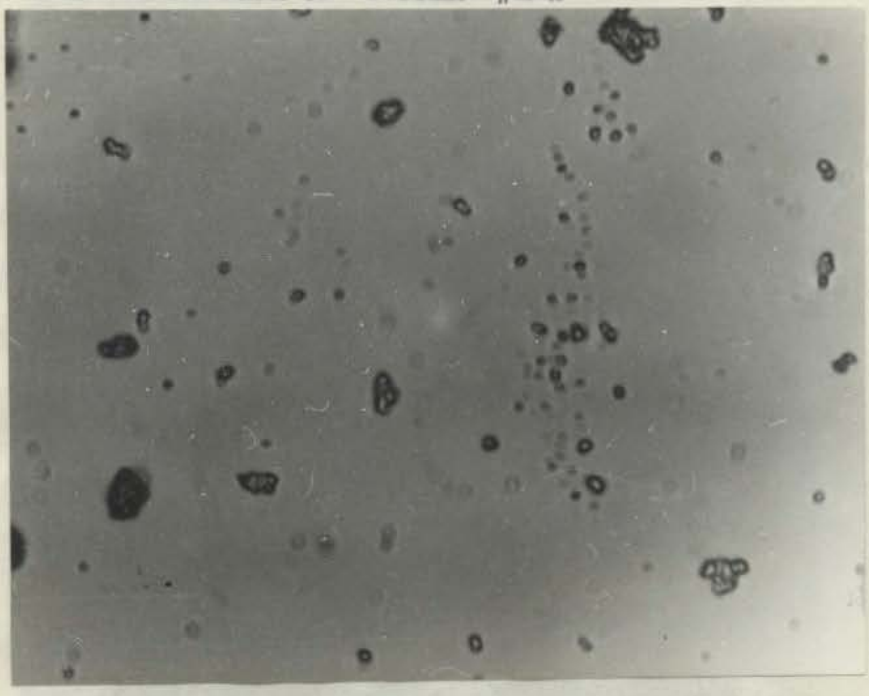
Chemical Composition:

The same as that given on p. 13.

Particle Size:

0.75 to 1.5 microns	85%
3 microns	10%
4.5 microns	3%
6 microns	2%
7.5 microns	1%
9 microns	1%

PHOTOMICROGRAPH OF "SUPREX" #x-2



ARC DUST #5914:

Chemical Composition: (24)

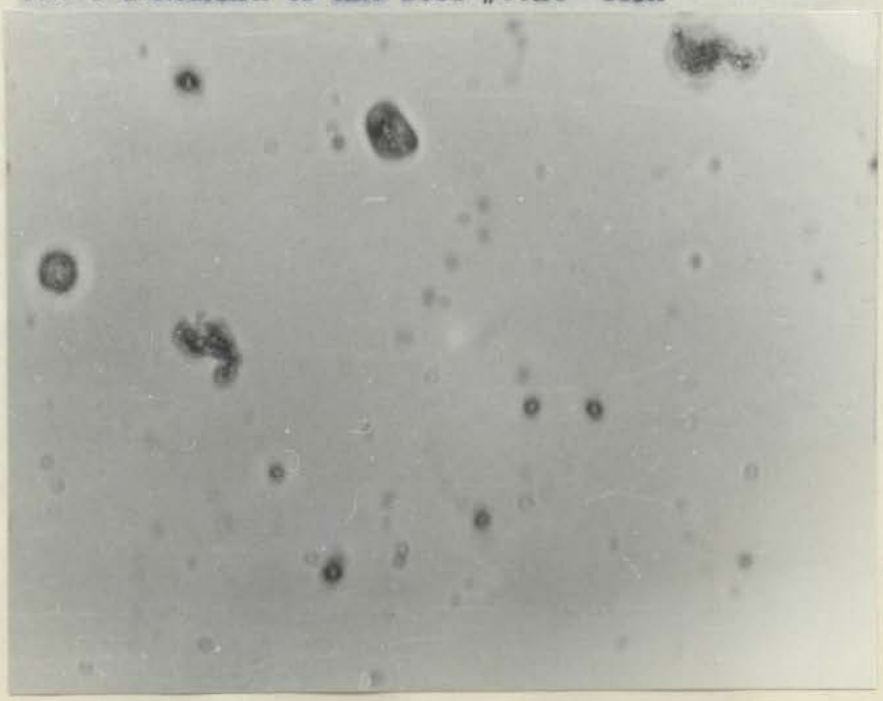
Calcium	0.5%
Fluoride	1.0%
Rare Earth oxides .	65.0%
Potassium	3.0%
Silica	10.0%

Carbon, Boron, and Sulphate are present in small amounts. There is no copper present.

Particle Size:

0.75 to 1.5 microns	86%
3 microns	9%
4.5 microns	2%
6 microns	2%
7.5 microns	1%

PHOTOMICROGRAPH OF ARC DUST #5914 440x



THERAPEUTIC ARC DUST #5967:

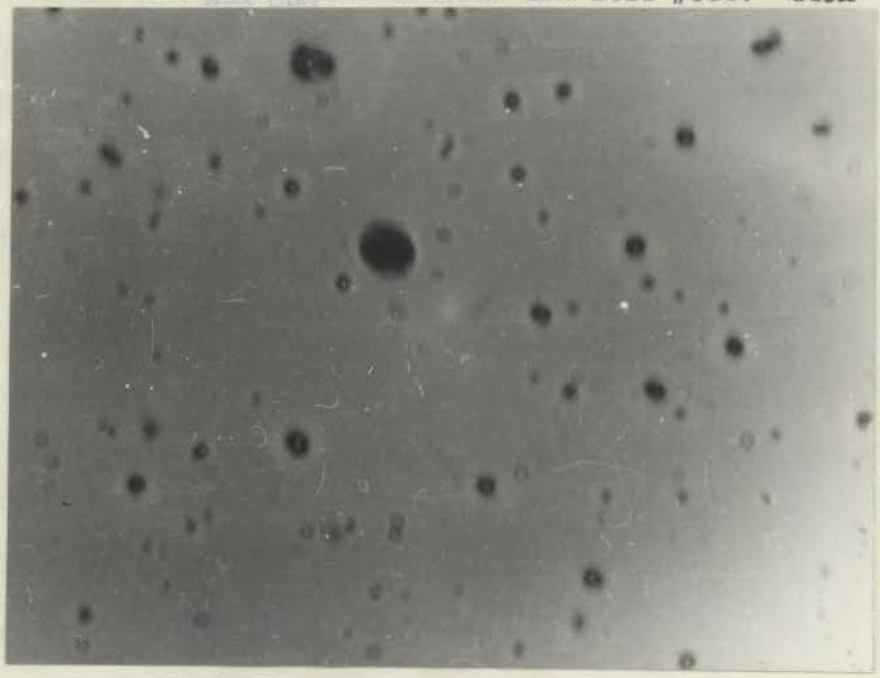
Chemical Composition: (24)

Fe_2O_3	...	46.1%
NiO	...	34.0%
Al_2O_3	...	11.6%
K_2O	...	2.2%
SiO_2	...	6.1%

Particle Size:

0.75 to 1.5 microns	82%
3 microns	13%
4.5 microns	3%
6 microns	2%

PHOTOMICROGRAPH OF THERAPEUTIC ARC DUST #5967 440x



CALCIUM PHOSPHATE:

Chemical Composition:

99% $Ca_3(PO_4)_2$

Particle Size:

0.75 to 1.5 microns	95%
3 microns	4%
4.5 microns	1%

COPPER OXIDE:

Chemical Composition:

99% CuO

Particle Size:

0.75 to 1.5 microns	79%
3 microns	10%
4.5 microns	4%
6 microns	3%
7.5 microns	2%
9 microns	1%

CALCIUM FLUORIDE:

Chemical Composition:

99% CaF_3

Particle Size:

0.75 to 1.5 microns	71%
3 microns	20%
4.5 microns	4%
6 microns	3%
7.5 microns	2%

The animals subjected to actual inhalation of dust were placed in a chamber having a volume of 2.3 cu. ft. Its design may be seen in the Photographic Supplement. Only the animals heads were actually in the dusting chamber. Concentrations of the dust varied from 12.8 mg./cu.ft. to 24.7 mg./cu.ft. The animals were exposed 3 hours per day 6 days a week for a period of 6 months at which time exposures were stopped. However certain of the animals were watched for as long as 9 months following the 6 months exposure. The results with these animals were not very satisfying. Apparently the animals were not exposed long enough or heavily enough.

The 45 rabbits used in this study were given 0.2 gm. of dust in 2 cc. of sterile physiological saline both intratracheally and subcutaneously. The chests of these animals were xrayed at 7 months and 10 months following administration of the dust. The x-ray findings could not be correlated with the necropsy findings. The disparity is attributed to the x-ray technique. The rabbits were killed 12 months after the dust had been administered. Microscopic sections of the viscera were made and stained with hematoxylin-eosin and Sharlach R stains. Tissue reactions to the dusts were then studied.

The 60 rats used in this study were given 0.2 gm. of dust in 2 cc. of sterile physiological saline intraperitoneally. Animals were killed at intervals of 15-30-60-90-200-360 days. Microscopic sections were made of the viscera. After staining the tissue reactions to the various dusts were studied.

The results of the study of tissue reactions of 16 dusts on 105 laboratory animals are summarized in Table I. The classification of the tissue reaction is that introduced by Gardner 1938 (25) (26).

TABLE I..CAPACITIES OF DUSTS TO PROVOKE TISSUE REACTIONS...SUMMARY EXPERIMENTAL OBSERVATIONS

	RABBITS-12mo.		RATS-Intraperitoneal (days)						MAXIMUM REACTIONS		
SUBSTANCE	INTRATRACHEAL	SUB-Q	15	30	60	90	200	360	RABBIT	RAT	TOTAL
Silica	5+	5+	5+	5+	5+	5+	5+	5+	5+	5+	5+
Coal (Bituminous)	+	2+	---	2+	3+	3+	4+	4+	2+	4+	4+
Iron Oxide	±	±	±	±	±	±	±	±	±	±	±
Talc	±	---	---	---	---	---	---	---	±	---	±
Suprex Mixture	3+	3+	---	---	---	---	---	---	3+	---	3+
Suprex #5643	3+	3+	---	---	---	---	---	---	3+	---	3+
Suprex #x-2	3+	3+	4+	4+	4+	5+	---	---	3+	5+	5+
Suprex #5913	3+	3+	4+	4+	4+	4+	4+	4+	3+	4+	4+
Suprex #5915	---	---	4+	4+	4+	4+	5+	5+	---	5+	5+
Suprex #5914	3+	3+	4+	4+	4+	5+	5+	5+	3+	5+	5+
Therapeutic Dust	+	+	3+	3+	3+	3+	3+	3+	+	3+	3+
Carbon	±	±	---	---	2+	---	---	---	±	2+	2+
Coke	±	±	---	---	3+	---	---	---	±	3+	3+
Calcium Phosphate	---	±	---	---	---	---	---	---	±	---	±
Cupric Oxide	±	±	---	---	---	---	---	---	±	---	±
Calcium Fluoride	±	---	---	---	---	---	---	---	±	---	±

Key for Table I.

± Reaction: Phagocytosis only, no reaction in the surrounding tissues.

1+ Reaction: Slightly irritating. Microscopic accumulations of lymphocytes in the immediate vicinity of dust cells.

2+ Reaction: Fixed connectivie tissue cells directly adjacent to dust cells irritated and there is slightly more evidence of chronic inflammation.

3+ Reaction: Non-progressive fibrosis. Injured connective tissue cells have begun to multiply as a result of irritation, but the proliferation does not progress far and remains localized in a zone close to the irritating particles.

4+ Reaction: More widespread fibrosis, which is suggestive of silicosis, but which has not attained mature hyaline form.

5+ Reaction: Represents the standard reaction to quartz. Functional cells of the organ injured and destroyed. Phagocytes migrate and concentrate the particles in focal areas. More tissue injured by this high concentration and fibrosis of a peculiar and characteristic type develops. Such fibrosis takes the form of nodules about the collected masses of silica.

6+ Reactions: Diffuse, non-nodular fibrosis.
7+

8+ Reaction: Acute inflammation. On irritant basis.

It may be gathered from Table I that:

1. Silica gives its characteristic proliferative reaction no matter what type of administration is used. The characteristic reaction is present as early as 15 days when the dust is administered intraperitoneally in the albino rat.

2. Bituminous coal gives various reactions under different methods of administration. These reactions range from 1 plus to 4 plus. The reaction in the peritoneal cavity reached the highest point of 4 plus in 200 days.

3. Hematite is quite inert in its action no matter what type of administration is used.

4. Talc is quite inert in action on lung tissue.

5. In regard to the carbon arc electrode dusts it may be seen that all the dusts are more inert in their action when administered by the intratracheal and subcutaneous routes in the rabbit than when they are administered by the intraperitoneal route in the albino rat. These differences in reaction could be due either to anatomic or species variation in reaction. Dust #5914 containing 10% SiO_2 gives a 5 plus reaction in the albino rat. Suprex dusts, #x-2, #5915, give a 5 plus reaction in the peritoneal cavity of the albino rat, while Suprex #5913 gives a 4 plus reaction under the same conditions. The Suprex dusts, #Suprex mixture, #5643, #x-2, #5913, #5915, all give a 3 plus reaction in the lung and subcutaneous tissues of the rabbit.

6. Therapeutic carbon arc dust is quite inert in the rabbit, but gives a 3 plus reaction in albino rats. It is the most inert of the carbon arc dusts.

7. Carbon and core materials (rare earth metals) are both inert in the rabbit, but give a 2 plus to 3 plus reaction respectively in the albino rat.

8. Calcium phosphate, copper oxide, and calcium fluoride are all inert.

Since carbon, core material, insoluble calcium, copper, fluoride, and iron are all found to be inert in their action the tendency of the arc dusts to cause the proliferative response in tissues must be attributed to the free silica present in the dusts. The silica content of the various carbon arc electrode dusts ranges from 2 to 10% approximately.

Certain of the carbon arc dusts, namely Suprex mixture, #5643, Suprex #x-2, #5915 caused acute death in both rabbits and albino rats in from 3 to 12 hours after injected in saline suspension. The belief, based on experimental evidence, is that the soluble cupric ion in the dust caused the death of the animals. If the dusts were washed several times in saline they were found to be no longer toxic. However the first filtrate from the washing upon injection was found to be acutely toxic. 0.2 gm. of these arc dusts contains about 6.25 mg. of soluble

cupric ion. Injection of the equivalent of 6.25 mg. of soluble cupric ion in the form of $CuSO_4$ produced acute death in animals in the same period of time as the unwashed dust samples and with the same pathological finding of hemorrhagic exudate in the bowel and erosion of the intestinal mucosa.

In the case of each of the above mentioned dusts the washed dust sample was used to study the chronic action of the dust.

GENERAL DISCUSSION — PNEUMOCONIOSES

OCCURENCE and EFFECTS

The conditions favoring the development of pneumoconiosis are frequently encountered in our modern industrial civilization. Those especially liable to develop pneumoconiosis are coal miners, both anthracite and bituminous, asbestos workers, hard rock miners, abrasive workers, granite workers, slate miners, iron miners and workers, pottery workers, and cement workers. Those engaged in industries where organic dusts are encountered show little tendency to develop pneumoconiosis. (27)

Not all of these pneumoconioses are equal in their seriousness. The relative dangers of the various dusts considered in this paper will be taken up in the discussions of the individual dusts. In any case recent work by Schnurer 1938 (28) of Pittsburgh who studied 342 autopsies at the City Hospital, Mayview, Pa., suggests that pneumonia, bronchitis, and emphysema rates increase in direct proportion to the degree of pneumoconiosis. Pancoast and Pendergrass 1931 (27) also state that those having pneumoconiosis are predisposed to bronchitis, pneumonia, and tuberculosis.

MECHANISM OF PRODUCTION OF PNEUMOCONIOSIS

In order for pneumoconiosis to develop certain dusts must be present in the atmosphere which the individual breathes. The respiratory tract by its curves and large surface area of moist

sticky mucosa is able to filter out considerable amounts of dust particles, but it has been shown by Lehmann 1935 (29) that there is retention of about 30 to 40% of the particles. Studies recorded by Bloomfield 1933 (30) show that most of the retained particles are between 1 to 5 microns in diameter. His work indicates that particles larger than 10 microns are not retained or do they reach the alveoli.

When the particles reach the alveolar spaces they are engulfed by "dust" phagocytes which are large mononuclear cells the origin of which is much disputed. Foot 1927 (31) believes that these dust phagocytes are monocytes of the blood. Gardner and Smith 1927 (32) believe that the dust phagocytes arise from the clasmocytes or histiocytes in the alveolar walls. Permar 1920 (33) believes that dust cells arise from the endothelium lining the capillaries in the alveolar walls. Hynes 1931 (8) believes that dust cells are derived from the alveolar epithelium.

In any case, no matter what the origin of these cells may be, the dust phagocytes engulf particles 10 microns in diameter and less and begin migration (27). The sequence of events which follows ingestion of the dust particles by phagocytes is as follows. The phagocytes penetrate the alveolar walls and pass into the tissue spaces. At a certain point at

the distal end of the alveolar ducts they enter the lymphatic channels. The lymphatics of the lung have been studied extensively by Miller 1937 (34). According to him the deep lymphatic channels begin at the distal end of the alveolar ducts. They follow the pulmonary veins and flow is from the periphery of the lung centrally toward the hilum. There are some superficial lymphatics of the pleura which drain the surface of the lung to a depth of 2 or 3 mm. These pleural lymphatics, though not passing through the lung transversely, eventually empty into the tracheo-bronchial lymph nodes. Along these lymphatic channels lymph nodes may be found. These nodes form a filter in which dust containing phagocytes may lodge. Lodging places may be found along the alveolar ducts, and the bifurcations of the bronchioles and bronchi. Larger nodes are found at the hilus and the tracheo-bronchial region. In any case, if dust phagocytes lodge in a node, the dust may kill the phagocytes and be liberated. Proliferation of the connective tissue begins in such areas. This fibrosis eventually results in blocking of the lymphatic channels draining into the particular involved node. Stasis in the channels makes lodging of other dust burdened phagocytes more probable. As a result there is aggregation of dust cells into groups and infiltration and proliferation of other cellular elements, all of which gives the characteristically

appearing nodular fibrosis. The dust phagocytes may die and liberate the dust. Other phagocytes pick up the dust and migrate to other areas. The process may go on and on. If the process continues the lymphatic channels are completely blocked and a diffuse interstitual fibrosis results. When the hilumward flow of lymph is greatly decreased the flow reverses toward the subpleural lymphatics. The same process is repeated and a peripheral nodulation results. Only silica gives this peripheral nodulation. It should be emphasized that the process described is an irreversible one and therefore the best treatment is prevention.

FACTORS AFFECTING THE DEVELOPMENT OF PNEUMOCONIOSIS

There are several factors which influence the development of the picture of pneumoconiosis just presented. As it was previously stated the chemical composition of the dust and the particle size of the dust are important considerations. The amount of dust inhaled per unit time has influence on the rapidity of development of a full blown pneumoconiosis. According to McCann writing in Cecil 1937 (36) it has been shown by Cummings of Saranac Lake that at 5 million particles/cu.ft. it takes 25 years or more for silicosis to develop. At from 15 to 20 million particles/cu.ft. it takes 15 to 20 years for silicosis to develop and at 100 million particles/cu.ft. it takes only 2 years for silicosis to develop.

In summary it is seen that the chemical composition, particle size, and amount of dust in the air as well as the length of time

of exposure are the important factors influencing the development of pneumoconiosis.

SYMPTOMS OF PNEUMOCONIOSIS

The symptoms of pneumoconiosis have been given by Singer 1938 (36) as dyspnea on exertion, lowered lung capacity, fever, nite sweats, and slight hemoptysis. The latter three symptoms are suggestive of the complicating condition of tuberculosis. McCain in Cecil 1937 (35) gives the symptoms of pneumoconiosis as shortness of breath on exertion, morning cough either dry or productive of mucoid sputum, and the physical signs as hyperresonance on percussion, diminished intensity of the breath sounds, scattered rales in the bases, and diminished circumferential expansion of the chest. Pancoast and Pendergrass 1931 (27) divided the symptoms of pneumoconiosis into those of the early stages and those of the late stages. In the early stages there may be dyspnea or nothing at all. In the later stages there are dyspnea, cough, cyanosis, fever, and loss of weight.

The roentgenologic appearance of the lungs in pneumoconiosis is of considerable importance in diagnosis. Pancoast and Pendergrass 1931 (27) divide the types of reactions seen into three stages.

Stage I. This stage represents the earliest abnormal condition encountered. There is increased prominence of the

hilar shadows, increased prominence and thickening of the truncal shadows and a greater prominence of the linear markings in the peripheral zone.

Stage II. A more advanced stage which shows distinctive distribution of small rounded densities varying in size from pin head to pea and distributed throughout both lungs.

Stage III. This is the most advanced stage. Three types may be differentiated: 1. Large masses of increased density formed from coalescence of large nodules of the 2nd stage. 2. There may be more or less diffuse fibrosis. 3. There may be massive fibrotic areas.

Most dusts aside from silica do not go beyond the Stage I. Excellent radiographs of silicotic chests and silico-tuberculous chests may be seen in the publication of Russel, et.al. 1929 (37)

DIAGNOSIS OF PNEUMOCONIOSIS

The diagnosis of this condition is based on an occupational history of exposure to dust, the symptoms enumerated previously, and the characteristic roentgenologic appearance of the lung. Examination of sputum for dust particles has not been of much value except in asbestosis certain asbestosis bodies are found.

IMPORTANCE OF LABORATORY METHODS FOR DETERMINING THE HARMFULNESS OF DUSTS

Since the processes in the development of pneumoconiosis are irreversible and since certain pneumoconioses predispose to grave diseases it is of utmost importance to have laboratory methods of determing the harmfulness of dusts. The techniques advanced by Gardner (19) (25), Miller and Sayers (12), and Kettle and Hilton (11) have been discussed in detail previously. It is by studying the tissue reactions of dusts in laboratory animals that newly encountered harmful dusts may be identified before they have given rise to irreversible changes in the lungs and reaped a large toll of human life to give clinical evidence of their harmfulness. Numerous lives were sacrificed to give clinical evidence of the harmful action of silica and silica containing dusts.

It was with the object of showing a relation between tissue reactions in experimental animals and clinical activity of dusts that the present experimental study was undertaken. How well these two things may be correlated will be seen in the discussions of the individual dusts which are to follow.

SILICA

Chemical and Physical Properties: Silicon the element is a non-metallic substance. It is not found free in nature, but in combination it is probably more widely distributed in the solid matter of the earth than any other element except oxygen. It comprises chemically about 27% of the earth's crust, oxygen about 46%. (38) It occurs chiefly as the oxide (SiO_2). Quartz, flint, rock crystal, amethyst, agate, jasper, and opal are rocks composed of SiO_2. It also occurs in combination with metallic oxides as silicates. Examples of this type of combination are granite, hornblende, asbestos, feldspar, clay, mica, talc, and soapstone. There are also fluosilicates of sodium, potassium, and zinc. (39) SiO_2 has been given the name "free silica". It is extremely hard and is insoluble in water.

For many years it was believed that the action of silica on tissues was due to its hardness and the sharpness of its particles. However it has been shown recently that silica (SiO_2) is soluble in the alkaline body fluids. King and McGeorge 1938 (40) give some interesting figures on the solubility of SiO_2 in body fluids.

Solubility of SiO_2 in Body Fluids
(mg. SiO_2/100cc.)

Days	1	2	3	5	12	18
Ascitic fluid	6.1	8.0	8.4	9.0	9.1	9.1
Blood Serum	2.1	3.4	4.5	5.8	8.7	8.9

They state that the smaller the particles the more rapid the SiO_2 goes into solution. This is altogether reasonable since the smaller the particle the greater the surface area exposed to the solvent. It is also of interest that they found that $Ca(OH)_2$, MgO, Fe_2O_3, $Al(OH)_3$, SrO, and $Be(OH)_2$ depress the solubility of SiO_2 in alkaline fluids.

SiO_2 is excreted in the urine. Normally there is 15 mg.% of SiO_2 in human blood and 0.8 to 2.2 mg. SiO_2/100 cc. excreted in the urine daily. In silicotics these figures are much higher. (41)

Histology of the tissue reaction: In the experimental animals, no matter if the silica was introduced intratracheally into the lungs, subcutaneously, or intraperitoneally, the lesions resulting were almost identical in appearance. The typical lesions produced are nodules composed of connective tissue proliferation. This proliferation is more or less in concentric zones of maturity, the least mature appearing peripherally. Scattered diffusely in the connective tissue many mononuclear phagocytes are seen. Particles are not seen in these phagocytes without the aid of polarized light. With the polarizing microscope the particles are easily seen. Infiltration with lymphocytes is characteristically seen. In the older nodules (6 months to 1 year) there is a

tendency to the formation of secondary connective tissue whirls within a nodule. In general hyaline degeneration and necrotic changes are seen in all of the more mature nodules.

In the livers of those albino rats receiving intraperitoneal injections of silica there are seen focal areas of nodule formation. These nodules are in a periportal position.

The histology of the tissue reaction to silica has been described by many authors and is essentially the same as that seen in the animals studied in this experiment. (42) (9) (43) Gardner 1937 (44) points out the similarity of the silicotic lesions to the lesions of tuberculosis. He states that at times it is difficult to differentiate between the two without the acid fast stain. Experimentally produced tissue reactions of silica are essentially similar to the clinical tissue reactions found at autopsy of silicotics. It is evident that animal experimentation can give valuable information on the harmfulness of silica containing dusts.

The Clinical Action of Silica: It has been pointed out in the general discussion the mechanics by which inhalation of dusts produces pneumoconiosis. In the case of inhalation of SiO_2 the pneumoconiosis produced is called silicosis. Just where does the harm arise from silica inhalation? It has been found clinically that the presence of silicosis is associated with an

increased morbidity and mortality from pulmonary tuberculosis. Gardner 1934 (45) writes that at least 75% of those humans who develop silicosis die of tuberculosis which may make its appearance at any stage of the disease.

It was previously stated that Kettle (6) showed that the tubercle bacillus proliferates in the rich tissue pabulum in silicotic nodules. Drinker 1936 (46) presents some interesting data from Collis on the incidence of death from tuberculosis occuring in individuals working in various concentrations of silica in the air.

Etiological Importance of Free Silica in Tuberculosis
From Collis of England

Occupation	% Quartz in Air	% Deaths from Pul. T.B.
Flint knappers	100	77.8
Grinders	50-100	49.7
Granite Cutters	30	47.8
Potters	20	18.9
Coal mining	-	9.8

It is of significance that the highest mortality from pulmonary tuberculosis occured in the group exposed to the highest concentration of silica. As the silica concentration in the air decreased there was a corresponding decrease in the percent of deaths from pulmonary tuberculosis.

Russel, et.al. 1929 (47) in his survey of granite workers gives some interesting figures which point out the increased mortality of silicotics from tuberculosis as compared to the general population.

Percent of Deaths in the Granite Industry Due to Tuberculosis 1900-1925 as Compared with All Occupied Males in the U.S. 1908-1909

Occupation	% Due to Tuberculosis
Cutters	65.6
Lumpers	52.0
Manufacturers and Dealers ..	50.0
Polishers	40.0
Occupied males	17.1

The 1900 United States census gives the death rate for tuberculosis in certain trades as follows: (48)

For miners and quarrymen 120.9/100,000

Stone cutters 540.5/100,000

Matz 1938 (49) reports autopsies on 23 silicotics. These were grouped as: Silicosis alone-5 cases, silicosis with non-specific lung infection-3 cases, silicosis with tuberculosis-14 cases, and silicosis with asbestosis-1 case.

From all the data presented in regard to increased death rates from tuberculosis in silicotics and the presence of tuberculosis in silicotics at autopsy, it is not difficult to see that silicosis is closely associated with pulmonary tuberculosis.

An excellent group of selected cases of silicosis and silico-tuberculosis taken from a study of over 500 cases of such conditions is presented by Russel, et.al. 1929 (50). In these cases diagnosis of silicosis was made on the following basis:

1. History of exposure to silica dust. History of fatigue, breathlessness, pleurisy pains, and slight cough.
2. Physical examination showing limited expansion of the chest (normal 7.7 cm.-silicotics 6.4 to 2 cm.), impaired resonance, diminished breath sounds, and increased fremitus.
3. Roentgenologic examination showing characteristic diffuse bilateral mottling.

Diagnosis of silico-tuberculosis was made on the basis of:

1. History of silica exposure, fever, hemoptysis, nite sweats, cough, and sputum.
2. Physical examination showing unilateral expansion of the chest, areas of dullness, increased fremitus, changes in breath sounds-bronchial breathing, and rales.
3. Positive acid fast bacilli in sputum.
4. X-ray findings.

In conclusion it may be said that silica is a harmful dust predisposing to tuberculosis. The tissue reactions produced experimentally in laboratory animals, and the appearance of the clinical reaction correlate beautifully.

BITUMINOUS COAL

Chemical and Physical Properties: The chemical composition of commercial bituminous coal has been given previously and it is apparent that carbon and oxygen comprise the larger proportion of the substance, i.e., about 75%. There is usually about 8% ash. Silica comprises about 0.8 to 3.5% depending upon the amount of hard rock mixed in with the coal. Coal being a hydrocarbon for the most part is insoluble in water.

Histology of the Tissue Reaction: There is less reaction to the intratracheal insufflation in the lungs and the subcutaneous injection than to the intraperitoneal injection. In general there is a slight tendency to encapsulation and nodule formation. The nodules are composed of dust phagocytes which contain black pigment. There is a varying degree of connective tissue trabeculation of the nodule. Lymphocytic infiltration is very sparse. There is no hyaline degeneration or necrosis. The reaction can be classified as a more or less non-progressive fibrosis.

Clinical Action: As far as the clinical activity of coal dust is concerned Cummins and Sladden 1930 (51) write that all experience in British observations point to the harmlessness of coal dust itself. However if previous silicosis has occured, blocking lymph channels, then there may be a serious result from coal on inhalation. They report 29 autopsies in coal miners in

which the lungs show general blackening (anthracosis). There are many consolidated black areas which cut with the consistency of india rubber. Microscopic examination of the lungs shows fibrosis, hyperplasia, and dust accumulation in the alveolar spaces, alveolar walls, perivascular, and peribronchiolar lymphatics.

Collis and Gilchrist 1928 (52) report findings on 426 English coal miners dying between 1910-1926. These men showed less tuberculosis than the general population, but they did have a higher death rate for bronchitis and pneumonia than the general population. Clinical observation by x-ray and necropsy examination of coal miner's lungs show that they are not normal, but they do not appear to have any increased incidence of tuberculosis.

In the case of coal the tissue reaction to experimentally introduced coal dust is found to be essentially similar to clinical findings. In general it may be said that both experimental tissue reactions and the clinical activity of coal dust is dependent upon the free silica content of the dust.

JEWELER'S ROUGE (HEMATITE)

Chemical and Physical Characteristics: Hematite or ferric oxide is a red insoluble compound. It is encountered in

hematite mining and in polishing operations where "red rouge" is used as an abrasive. Chemical analysis cited previously gives a content of 1.5% silica. Samples taken from various mines show considerable variation in the proportionate concentration of silica.

Histologic Appearance of Tissue Reaction: The lesions produced by intratracheal insufflation, subcutaneous and intraperitoneal injections are similar in appearance. They are small nodules thinly encapsulated. The nodules appear to be composed almost entirely of red pigment. This pigment is found to be present in phagocytes as well as lying free in the tissue spaces. There is no lymphocytic infiltration, fibrosis, or degenerative change. The reaction is essentially inert.

Clinical Activity: A clinical study of 100 hematite miners by Cronin 1926 (53) showed that there were some tissue changes in the lungs of the miners, but these changes did not predispose to bronchitis, pneumonia, or tuberculosis. On the other hand Stewart and Faulds 1934 (54) state that siderosilicosis results from inhalation of hematite containing large amounts of silica.

Naeslund 1938 (22) writes that no typical silicosis is evident in experimental animals exposed to four different Swedish iron ores containing 5% silica or less. On the other hand a relatively marked pneumoconiosis arose through the dust accumulat-

ing mainly intercellularly in greater or lesser cell aggregations without any sign of real fibrosis.

The tissue reactions produced experimentally showed iron oxide to be inert in its action. Clinical findings, except where there have been large concentrations of silica mixed with the iron oxide, have shown that iron oxide is not harmful. In the case of iron oxide we have a correlation between the experimental tissue reactions and the clinical activity of the dust. In either case the dust is essentially inert.

TALC (MAGNESIUM SILICATE)

Chemical and Physical Properties: Talc is grouped among the hydrous magnesium silicates. Other substances so grouped are soapstone and asbestos. These substances all have the formula $H_4(MgFe)_3Si_2O_9$. They differ in their physical structure however. Talc is insoluble in water.

Histology of Tissue Reaction: The intratracheal injection into rabbit lungs after 12 months shows microscopically several disseminated areas of phagocytic aggregation. These phagocytes are seen to contain some particles. There is no tendency to encapsulation of the areas. There is no round cell infiltration, fibrosis, or degenerative change. The reaction could be classified as inert.

Clinical Studies: Dreesen 1933 (55) reports a study on

57 talc miners. Clinical examination and x-rays of the chest were done on each man. He concludes that silicate dusts of trematite talc induce a fine diffuse bilateral fibrosis of the lungs which is definitely demonstrable by x-ray. While very dusty conditions prevail in certain departments of talc mining and preparation it cannot be said that the resultant pneumoconiosis has led to disability. It is only after 10 years exposure that the men begin to show 1st stage pneumoconiosis and the condition does not advance beyond this stage.

Fienberg 1937 (56) calls attention to the fact that talc granulomas have occured in operative incisions. He presents 5 cases in which the condition occured and he also presents data on the effect of injecting talc intraperitoneally into mice. He writes that nodules composed of granulomatous tissue and phagocytes containing crystals were present in 7 weeks.

Kronenberg 1937 (23) calls attention to the large amount of talc dust inhaled by nurses when dusting gloves. He believes that although studies have shown clinically that talc is not harmful, that precautions favoring less inhalation of talc should be taken.

Correlating the tissue reactions of talc produced by experimental introduction of the dust into laboratory animals with the clinical observations on the effect of talc inhalation

it is seen that in both cases evidence exists which would place talc in the non-harmful inert group of dusts.

CARBON

Chemical and Physical Properties: Carbon is encountered in smoke, coal, refining operations, and the manufacture of carbon products. The carbon used in this study was prepared by the precipitation of the carbon produced by burning crude oil. Carbon itself is insoluble in water.

Histology of the Tissue Reaction: Intratracheal insufflation into rabbit lungs, subcutaneous injection into rabbits, and intraperitoneal injection into rats showed the lesions produced to be nodules composed of phagocytes containing black particles. The tendency to encapsulation of the nodules is not great. There is no round cell infiltration, fibrosis, or degenerative change. The reaction is essentially inert.

Clinical Studies: Landis 1925 (57) writes that no organic dust causes pneumoconiosis. His study in particular involved 50 autopsies on textile workers. None of these individuals showed significant pneumoconiosis. More definite information on the action of carbon itself is given by Hollman 1928 (58). He examined a large number of workers who were exposed to carbon or graphite dust. They showed no evidence of pneumoconiosis in

5 years of exposure. However 9% of those working more than 5 years showed some evidence, though not marked, of fibrosis. He concludes that carbon or graphite dusts act in the same way as pure coal dust.

Both the experimental tissue reactions and the clinical observations on carbon dust appear to correlate well and indicate that carbon dust is not harmful.

CORE MATERIAL (RARE EARTH OXIDES)

Chemical and Physical Properties: The so called "core material" is used in the central cylinder of certain projection carbon electrodes. It serves to steady the arc stream and to give the light produced the proper spectrum and luminosity. As may be seen in the chemical analysis the core substance is composed of the oxides and fluorides of cerium, lanthanum, neodymium, praseodymium, and samarium. The oxides and fluorides of these substances are all insoluble in water and are quite inert chemically. Cerium comprises the greatest amount of the rare earth substances, i.e., 46%.

Histology of the Experimental Tissue Reaction: The experimentally produced lesions in the lung show scattered dust phagocytes in the alveolar walls and spaces, but no agglomerations of dust cells or any fibrotic reaction. Section through a hilar lymph node shows dust phagocytes in the periphery of the node, but no tissue reaction at all. The subcutaneous and intraperitoneal

lesions show nodules composed of agglomerates of dust phagocytes. There is definite, but slight encapsulation. Very little round cell infiltration and no fibrosis are seen. There are no degenerative changes. The reaction is essentially inert.

Literature on the Rare Earth Metals: There is no literature concerning the chronic tissue response to the rare earth substances. There is some data on the acute and chronic toxicity of these substances however. Maxwell and Bischoff 1931 (59) give the intravenous toxic doses for rats of the chloride salts:

Cerium ..... 50-60 mg./kg.

Praseodymium ..... 3.5-4.5 mg./kg.

Dryfuss and Wolf 1906 (60) studied the acute and chronic effects of lanthanum, praseodymium, and neodymium. Using the chloride salts they found that acutely 0.1 gm. of any one of the substances would kill a 440 gm. guinea pig in 20 hours with convulsions. In studying the chronic effects they gave 20 mg./kg. doses every day for 43 days into the peritoneal cavities of rats and guinea pigs. These animals showed no weight loss and on section the only abnormality was an induration at the sites of injection in the peritoneal cavities.

Steidel 1935 (61) gives the most comprehensive summary of man's knowledge concerning the rare earth substances.

General statements which may be obtained from his work are: The salts of the rare earth metals are relatively slightly toxic to warm blooded animals because they are poorly absorbed. In subcutaneous injection of the metals there frequently arise local hyperemia, hemorrhages, and tissue necrosis. The toxic doses for the various metals on different animals when given subcutaneously are as follows:

The MLD for Albino Mice, Rats, and Guinea Pigs
(gm./kg. subcutaneously)

Substance	Mice	Rats	Guinea Pigs
Cerium chloride	5-10	2-4	-
Lanthanum chloride	3-5	-	-
Neodymium chloride	-	.15-.25	-
Praseodymium chloride	.9-1.5	2	-
Samarium chloride	-	2	.75-1.0

As was stated before there is no data on the chronic effects of these substances on tissues. In like manner there is no data on the clinical effects of inhalation of rare earth dusts. Based upon the experimental tissue reaction it may be said that the rare earth oxides in the dust would not prove ppoliferative or harmful if they were inhaled.

CALCIUM PHOSPHATE, CUPRIC OXIDE, AND CALCIUM FLUORIDE

Physical and Chemical Properties: These substances were studied to see the effect of insoluble compounds of calcium, copper, fluoride, and phosphate on tissues. The three salts used are all insoluble in water.

Histologic Appearance of the Tissue Reaction: Only intratracheal insufflation and subcutaneous injections were done. The intraperitoneal injection was not done in any case. In the cases of all the dusts the reactions were very inert. Calcium phosphate in the lung at the end of 12 months showed scattered dust phagocytes in the alveolar spaces and alveolar walls with no tendency to aggregation of the phagocytes. Cupric oxide showed essentially the same picture. Section of the hilar lymph node showed dust phagocytes in the periphery, but no fibrosis. Calcium fluoride appeared very much like the calcium phosphate. In the case of none of these dusts were fibrosis, round cell infiltration, or degenerative changes observed.

There is no clinical data on the effects on inhalation of any of these substances. It could be predicted from their tissue reactions that they would be quite inert clinically.

CARBON ARC DUSTS

Chemical and Physical Properties: It may be seen from the chemical analyses given previously that dust which is encountered in motion picture projection electrodes is composed for the most part of rare earth oxides. Fluorides comprise approximately 10-12% of the dust substance. The fluoride exists in combination with the rare earth metals and as such is insoluble in water. Iron oxide, SiO_2, potassium oxide, and sulphur trioxide are present in concentrations from 1.5 to 3%. Calcium oxide, phosphorus pentoxide, boric anhydride, manganese oxide, copper oxide, and unburned carbon are present in very small quantities.

All of the suprex dusts, i.e., #5643, #5915, #5914, #x-2, and # Suprex Mixture have essentially the same chemical composition. Dust #5914 is essentially similar, but contains 10% SiO_2. Information on the chemical composition of the Therapeutic arc dust was not obtainable, except that it contains iron oxide, aluminum, and nickel in small quantities.

Histology of the Tissue Reactions: This is best presented in the form of a table.

Table Showing Maximum Tissue Reactions
of Carbon Arc Dusts*

Dust	Rabbit Lung and Sub-Q	Rat Intraperitoneal
Suprex Mixture	3+	Not done
Suprex #5643	3+	Not done
Suprex #x-2	3+	5+
Suprex #5913	3+	4+
Suprex #5915	Not done	5+
Suprex #5914	3+	5+
Therapeutic #5967	1+	3+

*For key see Table I.

In every case the suprex dust samples gave the same tissue reaction in the lung and in the subcutaneous tissues of the rabbit. Section of the lesions produced shows encapsulated areas of dust phagocytes. There is a slight tendency to localized fibrosis and some round cell infiltration. There are no degenerative changes.

Intraperitoneal injection into rats showed a more violent reaction in every case. For the most part microscopic sections show evidence of marked fibrotic response as early as 30 days after injection. The omentum, mesentaries, and ventral abdominal wall show nodules composed of dust phagocytes well encapsulated and with marked fibrosis within the nodules. As the lesions progress

from 15 days to 360 days evidence of a more mature appearance of the connective tissue cells is seen. In the older lesions, i.e., 60 days and above, hyaline degeneration and necrosis are frequently seen. Varying degrees of round cell infiltration are seen in every nodule. The livers of several of the rats receiving intraperitoneal injection show focal nodules of fibrosis in the periportal position. These liver lesions may be due to lymphatic drainage from the omentum into the liver. The reaction to these suprex dusts is essentially proliferative.

The therapeutic dust was found to be quite inert in its tissue reaction. There was only a slight tendency to encapsulation of aggregates of dust phagocytes in the rabbit's lungs. The subcutaneous nodules in the rabbit show a definite capsule about nodules composed of dust phagocytes. There is no fibrosis, round cell infiltration or degenerative change evident. The intraperitoneal lesions in rats showed nodules composed of dust phagocytes, slight round cell infiltration, and slight fibrosis, but no degenerative changes. The reaction to this dust is essentially inert.

Why the suprex arc dusts cause such a marked tissue reaction in the peritoneal cavity of the albino rat is not clear. The component substances of the dust; the rare earth oxides, carbon, iron oxide, insoluble calcium salt, insoluble phosphate salt,

insoluble copper oxide, and insoluble fluoride salt administered individually under the same conditions as the suprex dusts, were all found to be more or less inert in their actions on tissues. However it must not be forgotten that silica is present in the arc dusts, though in small concentration. It is conceivable in no other way except that SiO_2 in the arc dust is responsible for the reaction since all other constituents are inert and it is known that silica is proliferative in its action.

There is no other data on the tissue reactions of the arc dusts or upon their clinical action so correlation of tissue reactions with clinical activity is not possible in the cases of these dusts.

Since it is observed by tissue reactions that these dusts are proliferative it is possible that if they were inhaled in sufficient quantities over long enough periods of time they might cause a harmful pneumoconiosis, however we know of no conditions where the concentration of the arc dust in the atmosphere would reach levels high enough to produce such pathology.

In any case nevertheless it is recommended that proper and efficient ventilation of any closed space where these dusts are in the air should be done. If ventilation of projection booths

is sufficient to get ride of the harmful nitrogen oxides which are formed during arc combustion there should be no danger of the dust reaching harmful concentrations. (62) (63) (64) (65)

CONCLUSIONS

1. It is possible to correlate tissue reactions of dusts when administered to laboratory animals by the intratracheal, subcutaneous, and intraperitoneal routes with the clinical activities of the dusts.

2. Of the dusts studied: a. Silica (SiO_2) and certain of the Suprex arc dusts were found to be proliferative. b. Bituminous coal, certain of the carbon arc dusts, iron oxide, talc, carbon, certain rare earth metals, calcium phosphate, cupric oxide, and clacium fluoride were found to be essentially inert in various gradations.

3. The tissue reaction in the peritoneal cavity of the albino rat was found always to be slightly more violent than the reaction either in the lung or the subcutaneous tissues of the rabbit.

4. The tendency to proliferation observed in certain of the Suprex arc dusts is attributed to their silica content.

5. It is recommended that atmospheres containing dusts from the carbon arc lamp be properly ventilated and the dust concentration kept to a minimum.

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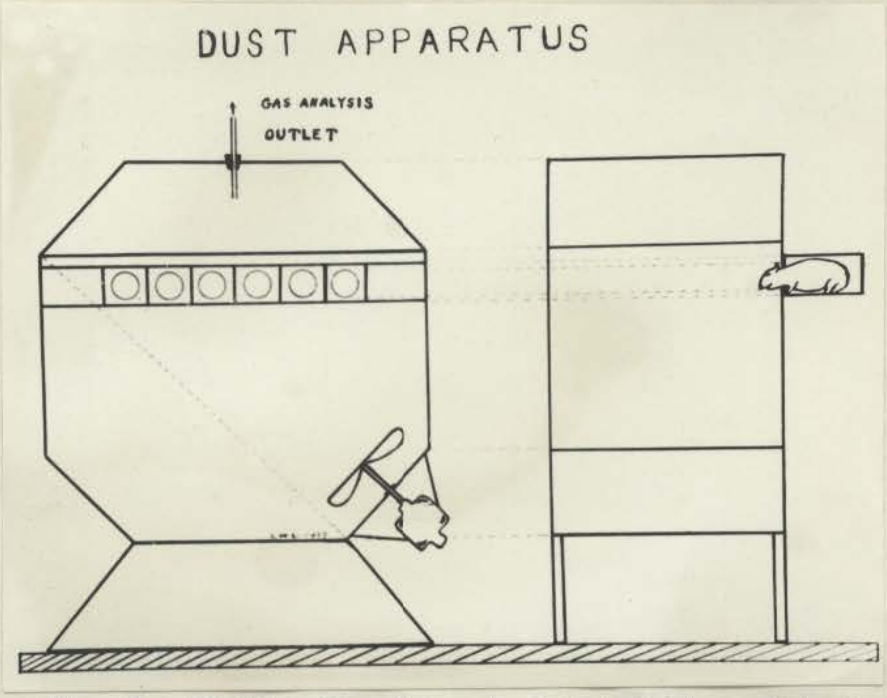

Fig. 1. Dusting Box for actual inhalation of dusts.

Fig. 2. Silica 15 days. Rat. Intraperitoneal Injection.

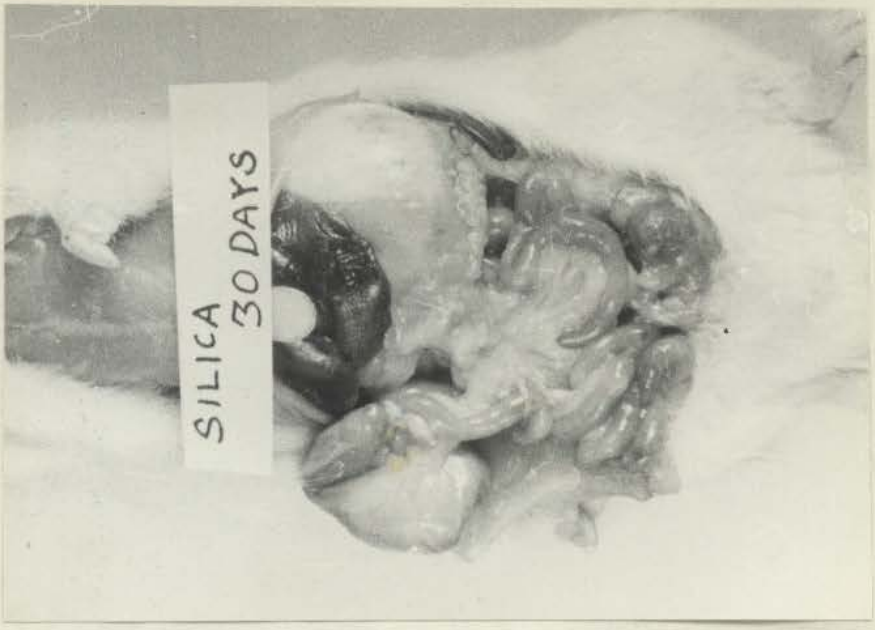

Fig. 3. Silica 30 days. Rat. Intraperitoneal Injection.

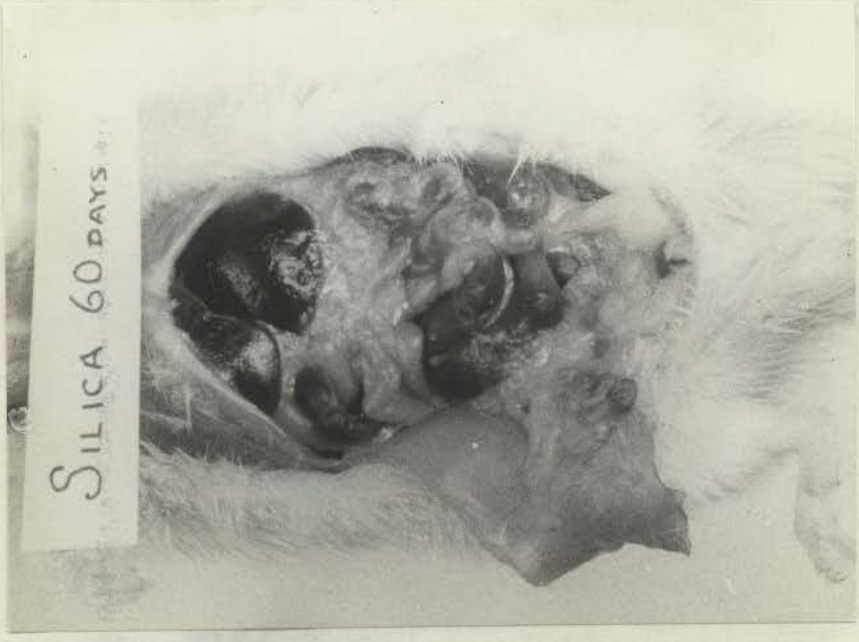

Figure 4. Silica 60 days. Rat. Intraperitoneal Injection.

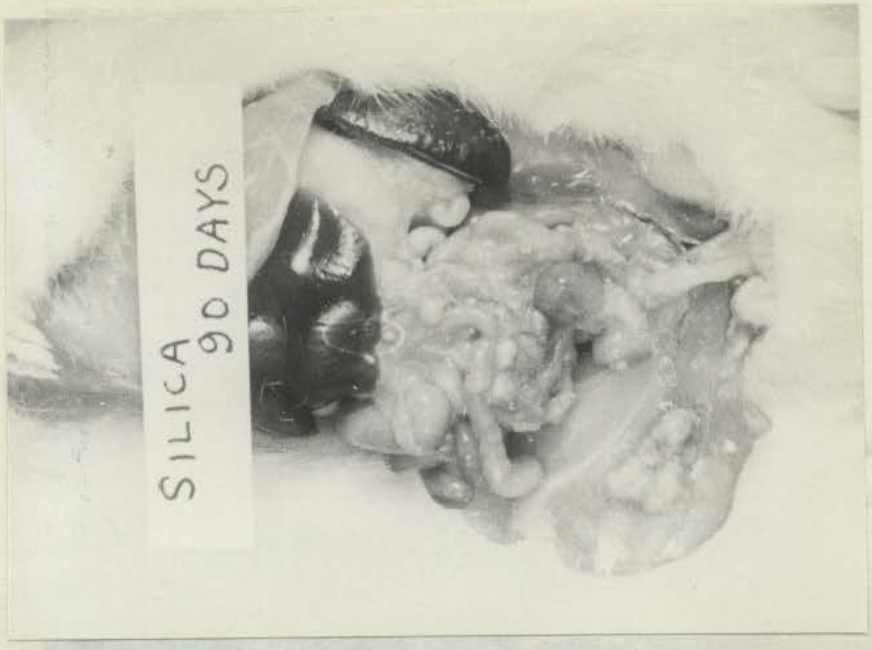

Fig. 5. Silica 90 days. Rat. Intraperitoneal Injection.

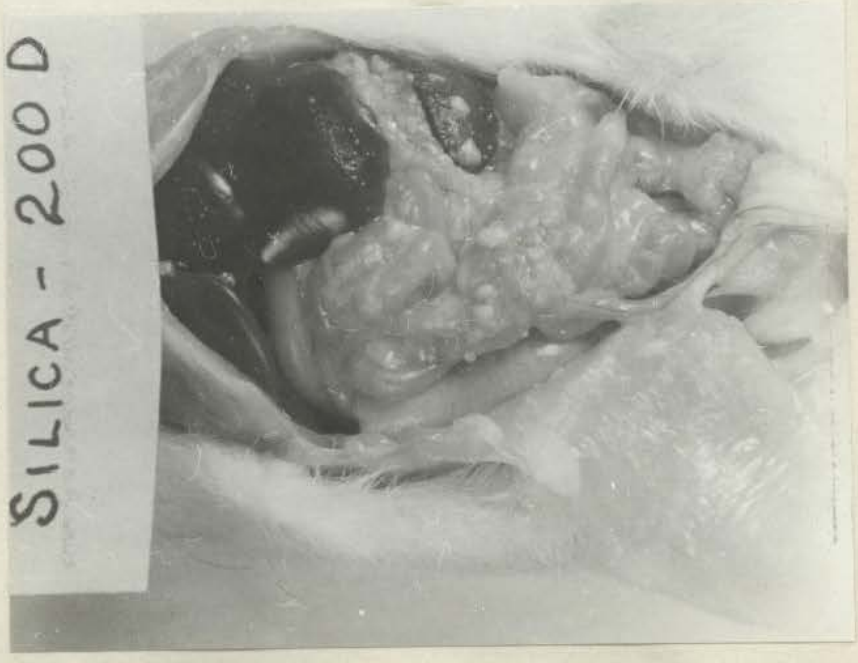

Fig. 6. Silica 200 days. Rat. Intraperitoneal Injection.

Fig. 7. Silica 360 days. Rat. Intraperitoneal Injection.

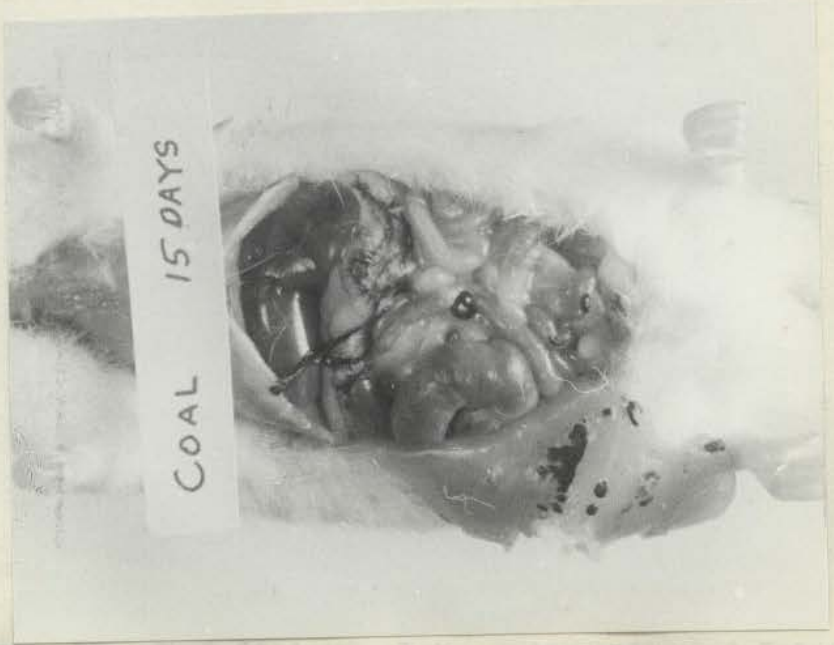

Fig. 8. Coal 15 days. Rat. Intraperitoneal Injection.

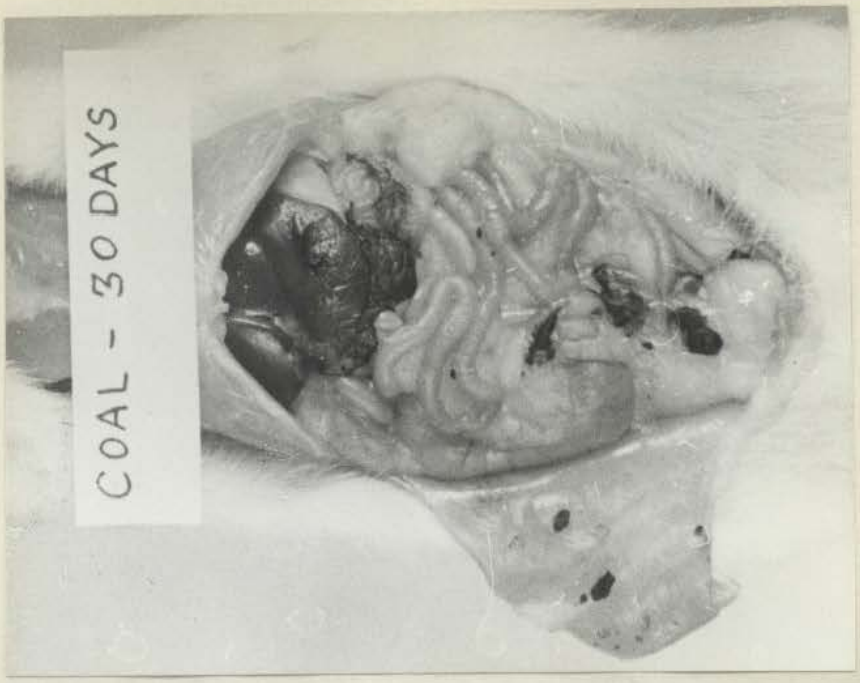

Fig. 9. Coal 30 days. Rat. Intraperitoneal Injection

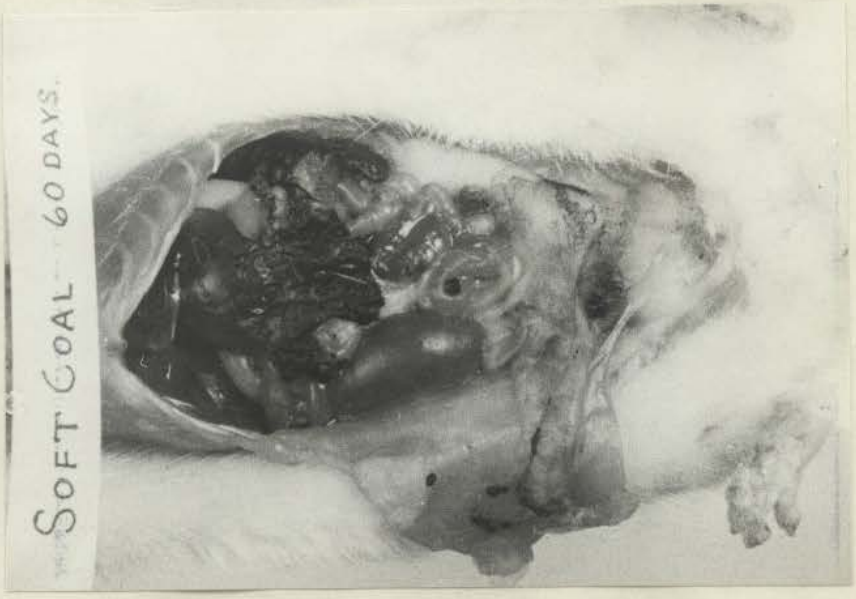

Fig. 10. Coal 60 days. Rat. Intraperitoneal Injection

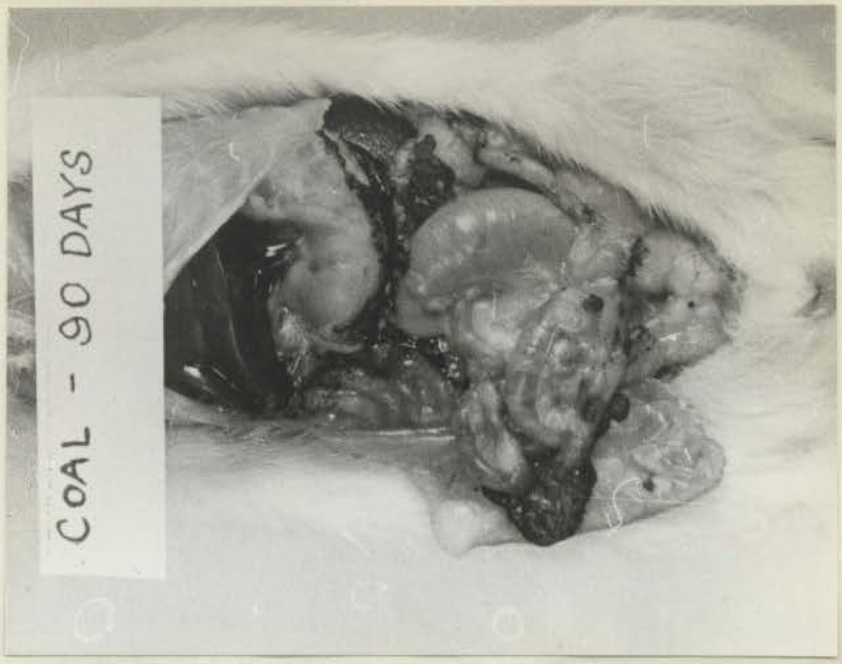

Fig. 11. Coal 90 days. Rat. Intraperitoneal Injection

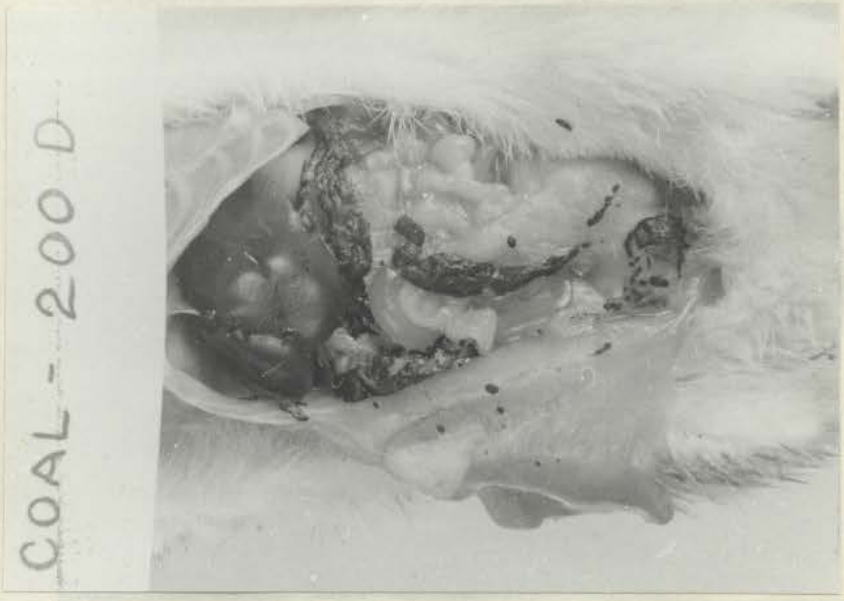

Fig. 12. Coal 200 days. Rat. Intraperitoneal Injection

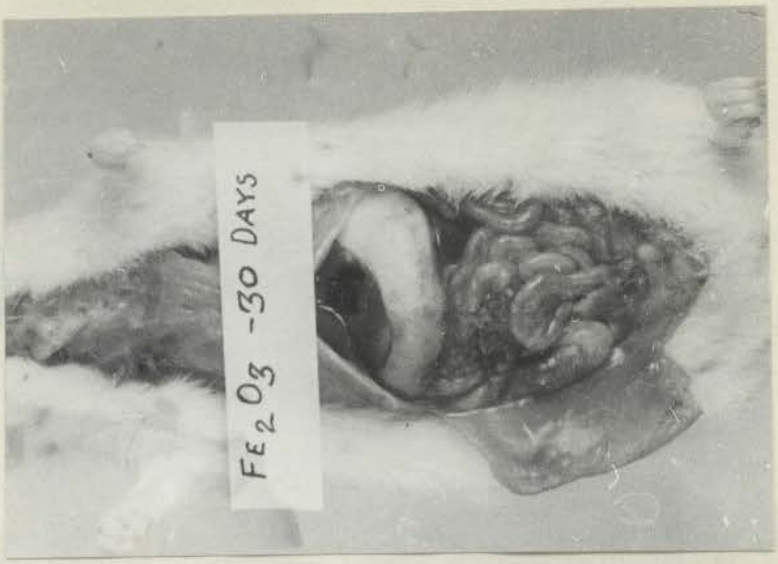

Fig. 13 Hematite.30 days. Rat. Intraperitoneal Injection

Fig. 14. Hematite 360 days. Rat. Intraperitoneal Injection

Fig. 15. Therapeutic Carbon Arc Dust 30 days. Rat. Intraperitoneal Injection.

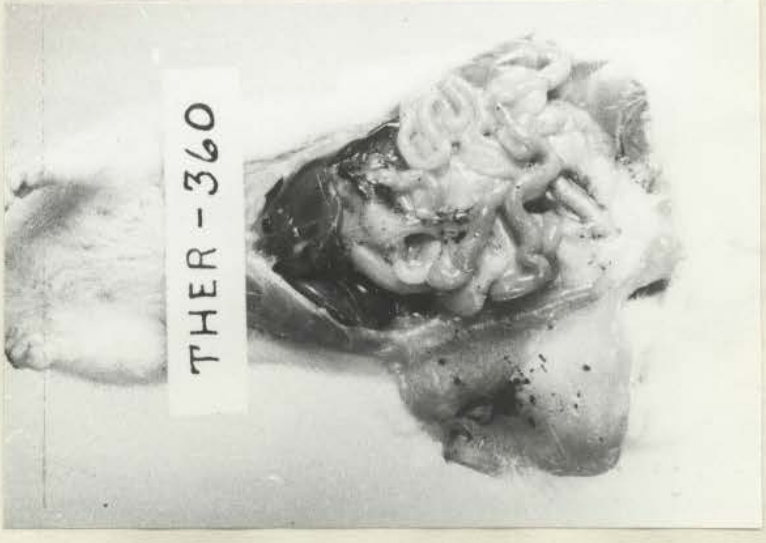

Fig. 16. Therapeutic Carbon Arc Dust 360 days. Rat. Intraperitoneal Injection.

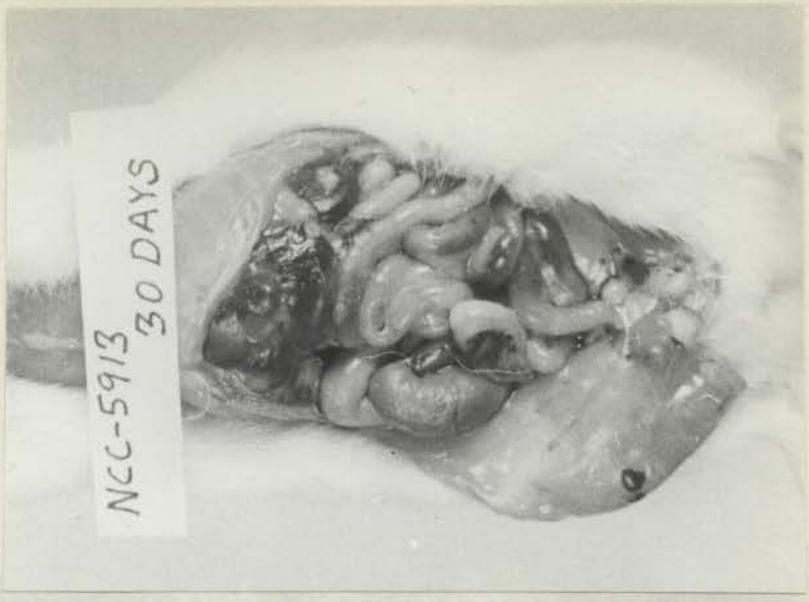

Fig. 17. Suprex Carbon Arc Dust #5913. 30 days. Rat. Intraperitoneal Injection.

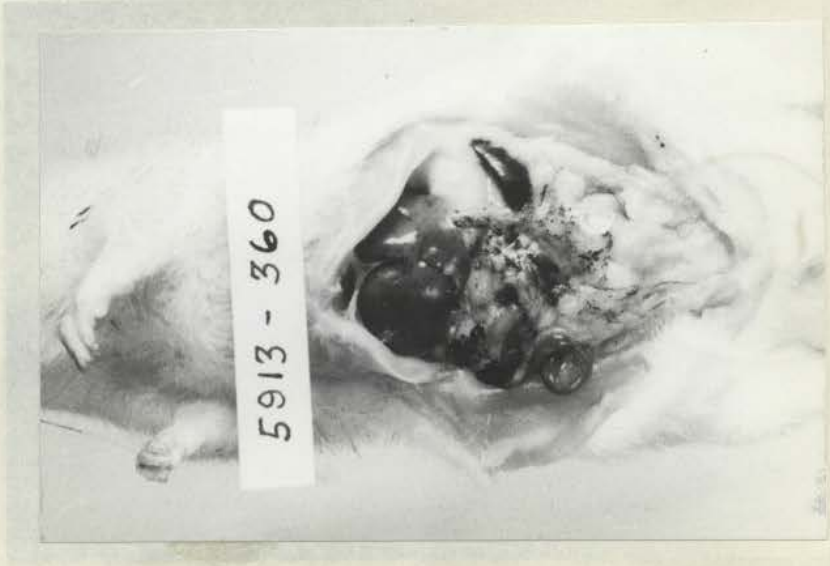

Fig. 18. Suprex Carbon Arc Dust #5913. 360 days. Rat. Intraperitoneal Injection.

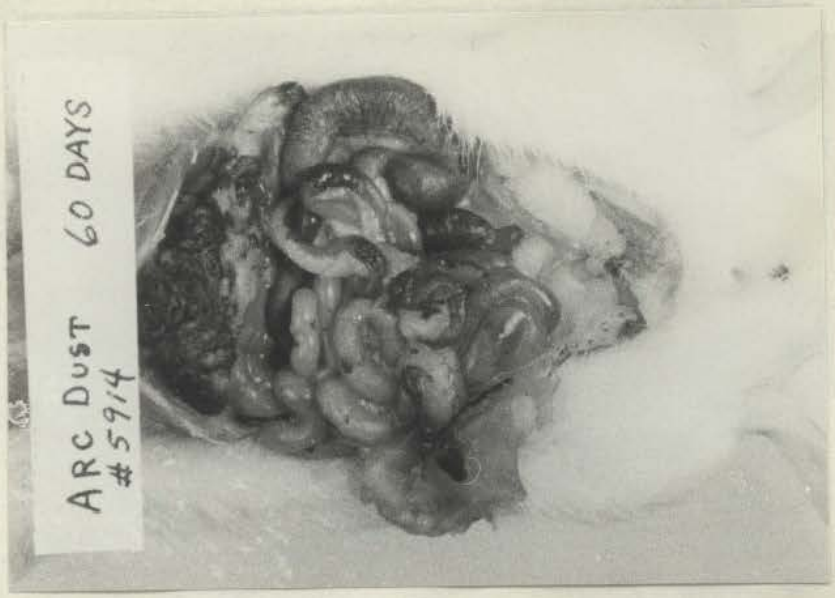

Fig. 19. Suprex Carbon Arc Dust #5914. 60 days. Rat. Intraperitoneal Injection.

Fig. 20 Suprex Carbon Arc Dust #5914. 360 days. Rat Intraperitoneal Injection.

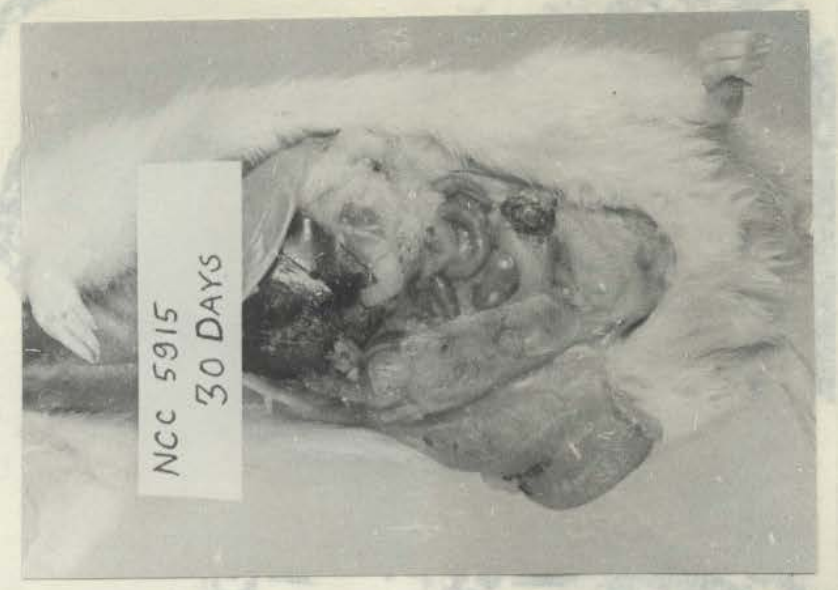

Fig. 21. Suprex Carbon Arc Dust #5915. 30 days. Rat. Intraperitoneal Injection.

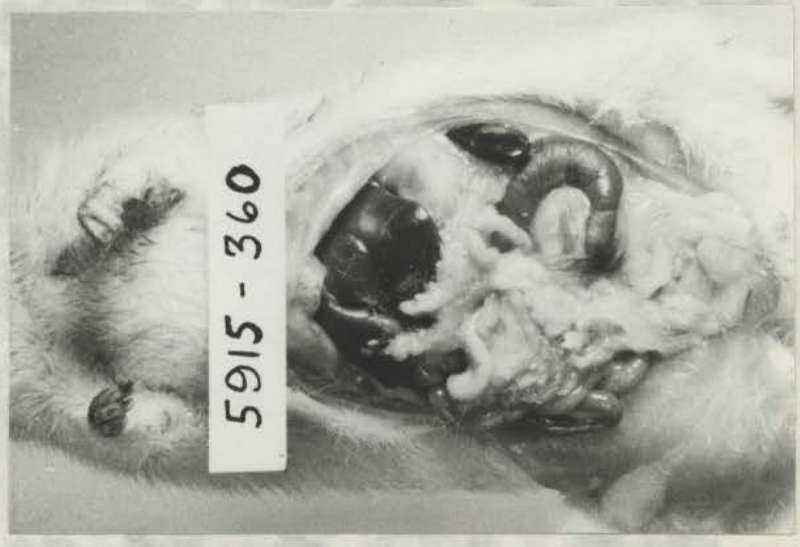

Fig. 22. Suprex Carbon Arc Dust #5915. 360 days. Rat. Intraperitoneal Injection.

Fig. 23. Silica. Rabbit 12 months. Lung. 100x
Showing silicotic nodule. Notice round cell infiltration.

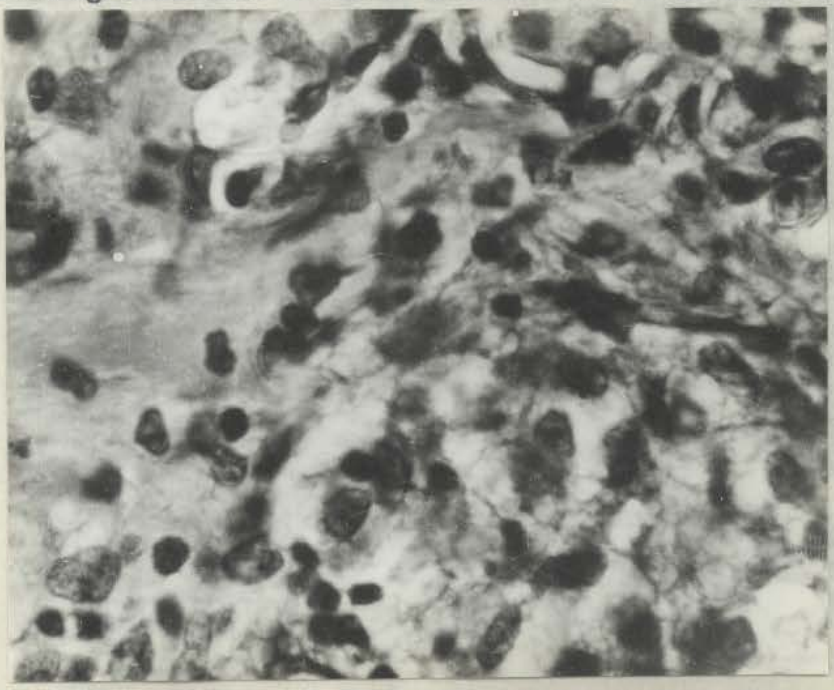

Fig. 24. Silica. Rabbit 12 months. Lung. 440x
Showing fibrosis and round cell infiltration.

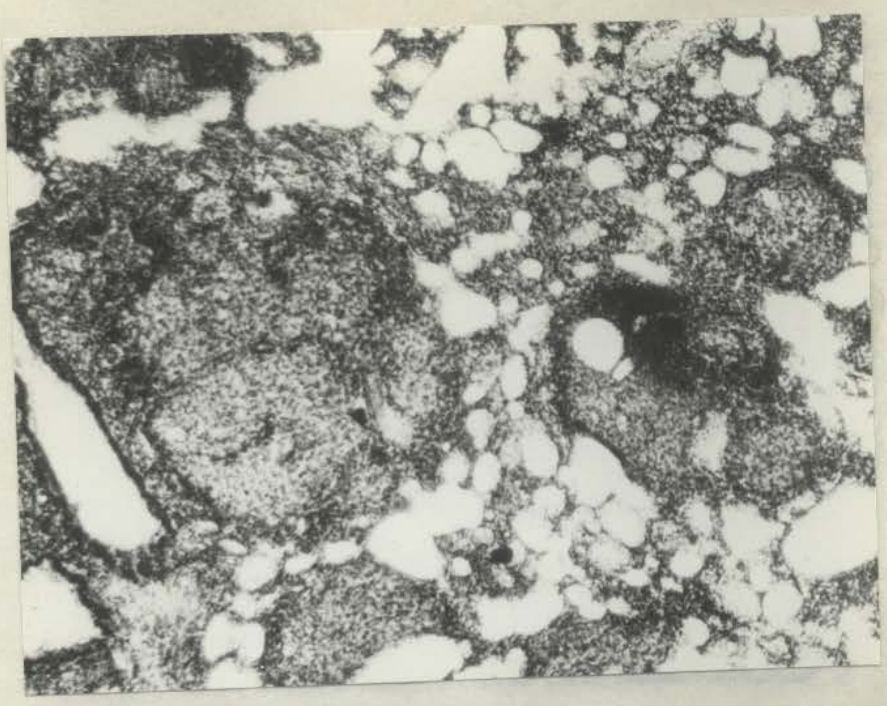

Fig. 25. Silica. Rabbit 6 months. Lung. 40x
Showing multiple silicotic nodules. Note density of tissue.

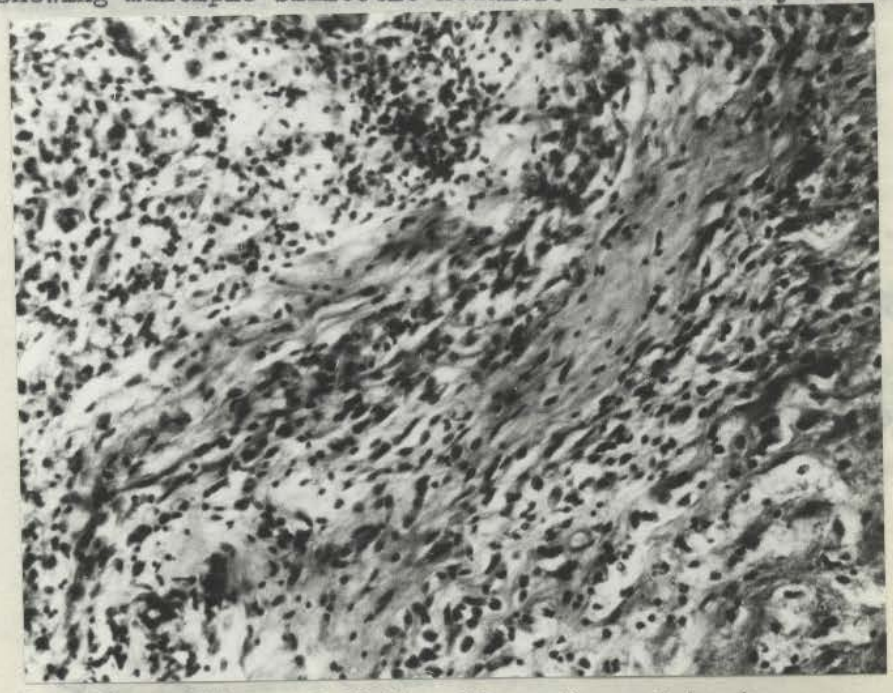

Fig. 26. Silica. Rabbit. 12 months. Subcutaneous nodule. 100x. Portion of nodule showing round cell infiltration, fibrosis, and beginning hyaline degeneration.

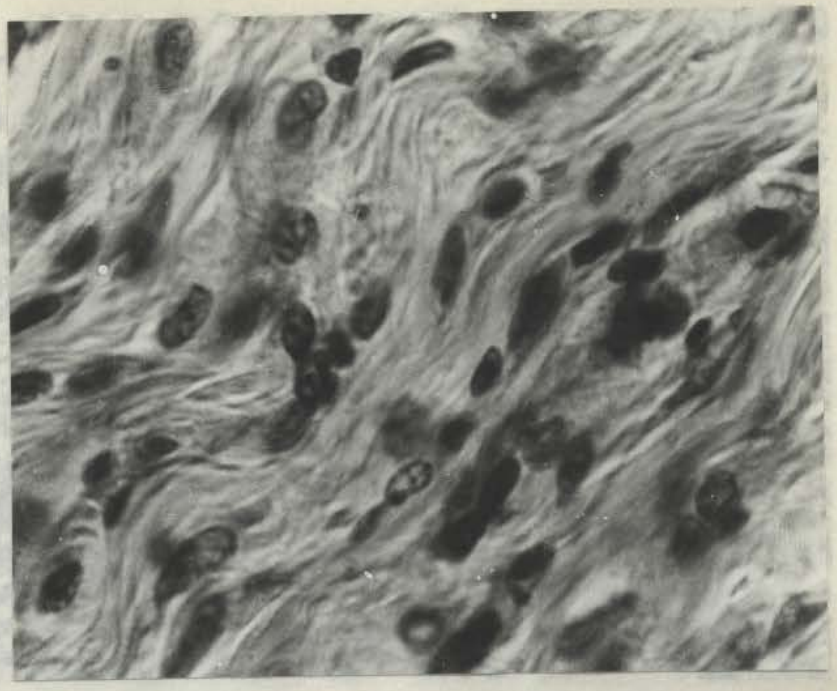

Fig. 27. Silica. Rabbit 6 months. Subcutaneous nodule. 440x. Portion of nodule showing characteristic type of fibrosis.

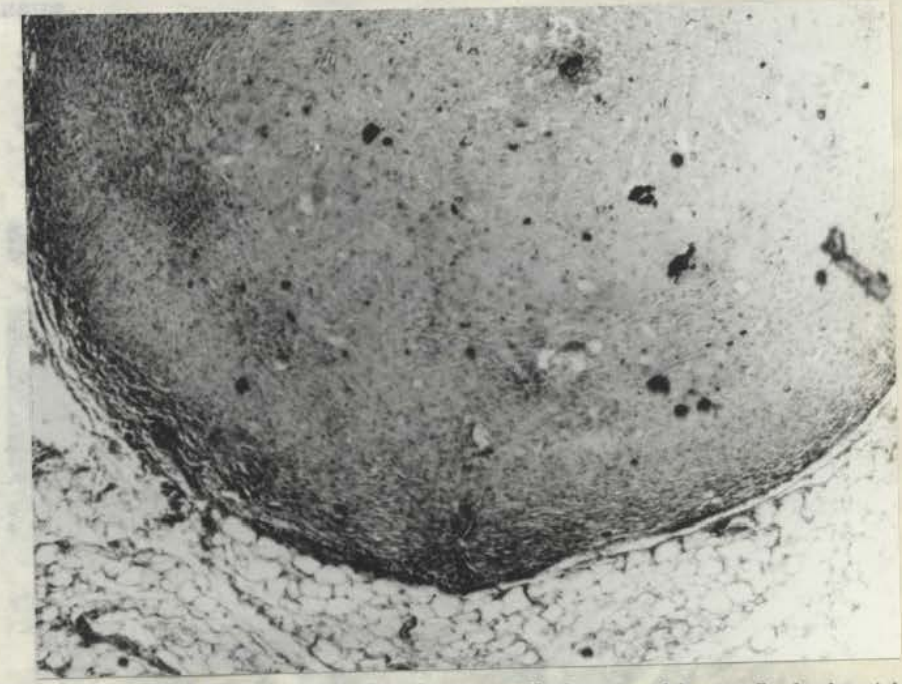

Fig. 28. Silica. Rat 60 days. Intraperitoneal injection. 40x. Showing portion of silicotic nodule in omentum. Observe density of tissue and also mature fibrosis centrally and recent fibrosis peripherally.

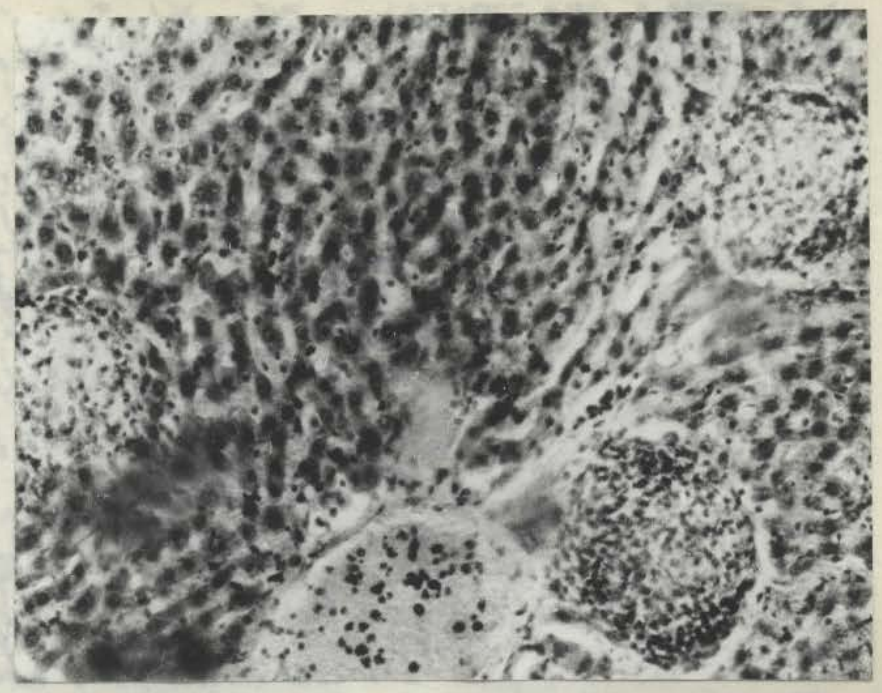

Fig. 29. Silica. Rat 200 days. Intraperitoneal injection. 100x. Liver: Showing marked hyaline degeneration of fibrotic tissue.

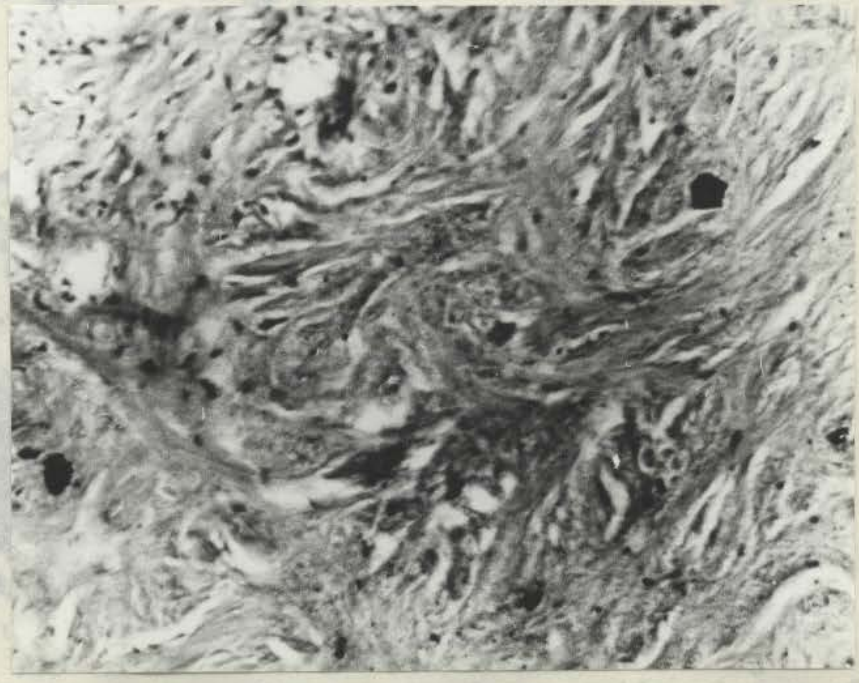

Fig. 30. Silica. Rat 360 days. Intraperitoneal injection. 100x. Portion of silicotic nodule showing marked hyaline degeneration of fibrotic tissue.

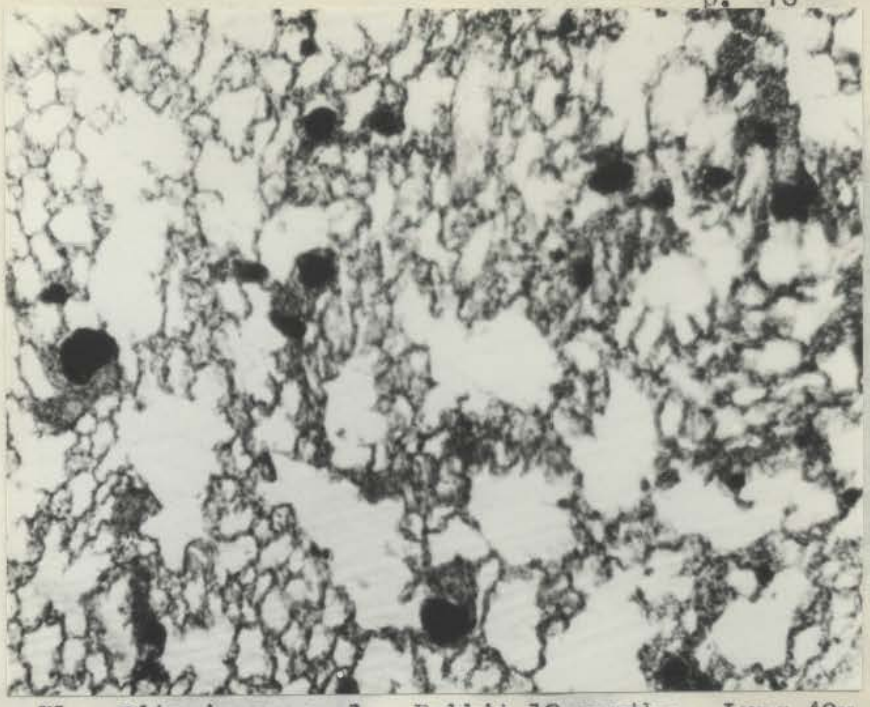

Fig. 31. Bituminous coal. Rabbit 12 months. Lung 40x Showing distribution of coal aggregations in the lung.

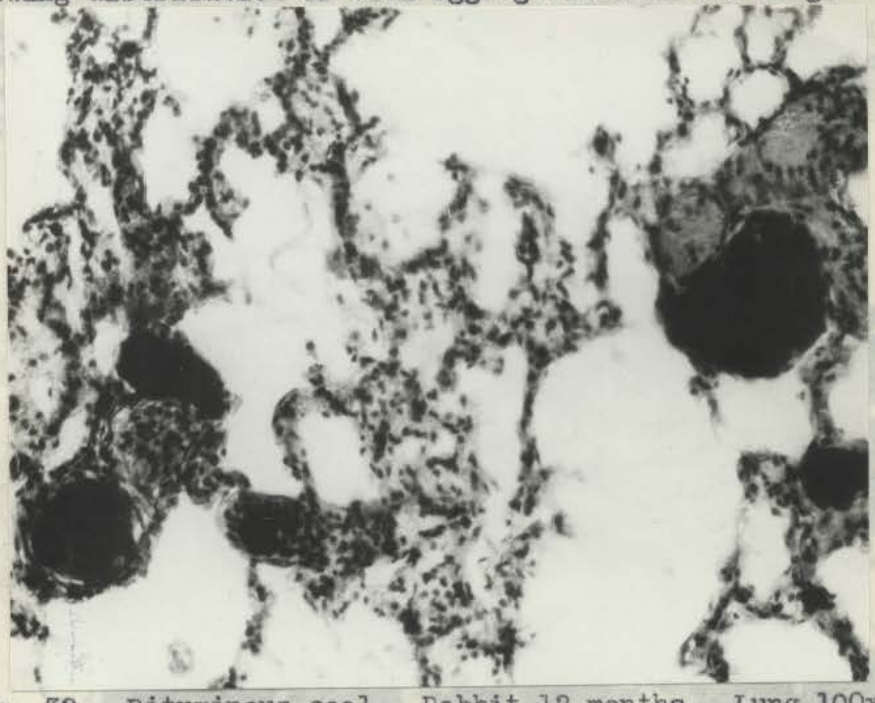

Fig. 32. Bituminous coal. Rabbit 12 months. Lung 100x Showing coal aggregations in the lung. Notice absence of fibrosis, round cell infiltration, and degenerative changes.

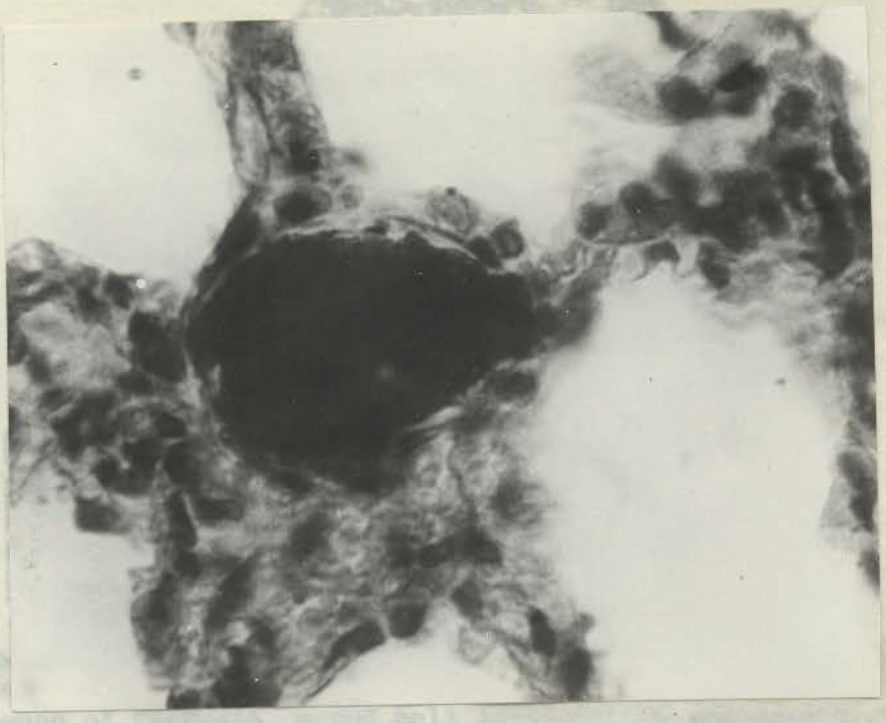

Fig. 33. Bituminous coal. Rabbit 12 months. Lung. 440x Showing detail of coal aggregation in lung. Notice fineness of capsule and absence of round cell infiltration, fibrosis or degenerative changes.

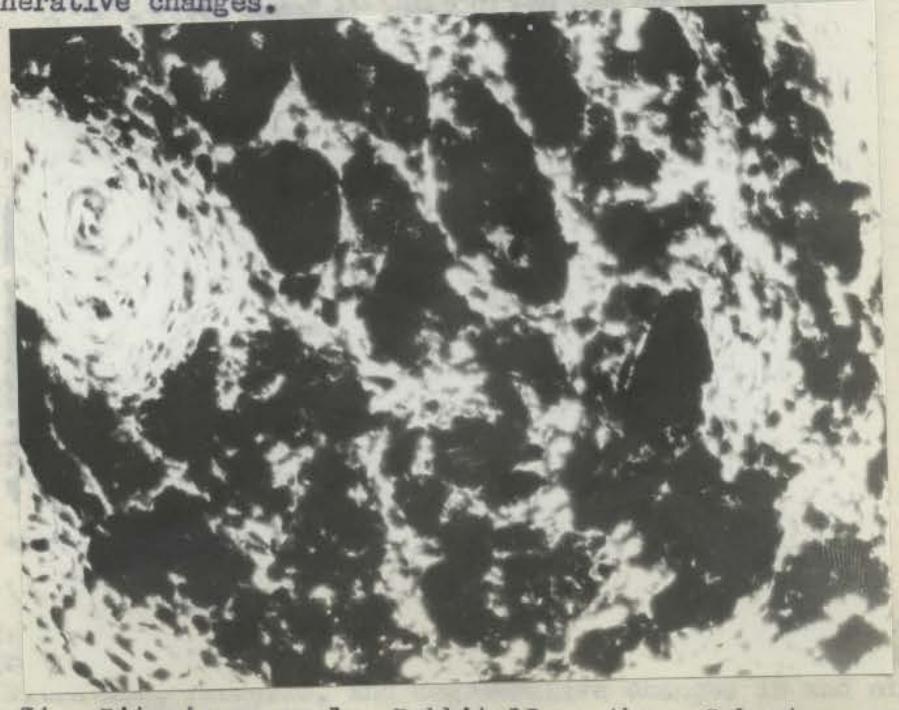

Fig. 34. Bituminous coal. Rabbit 12 months. Subcutaneous nodule. 100x. Showing portion of the nodule. Notice absence of fibrosis and lack of round cell infiltration or degenerative changes.

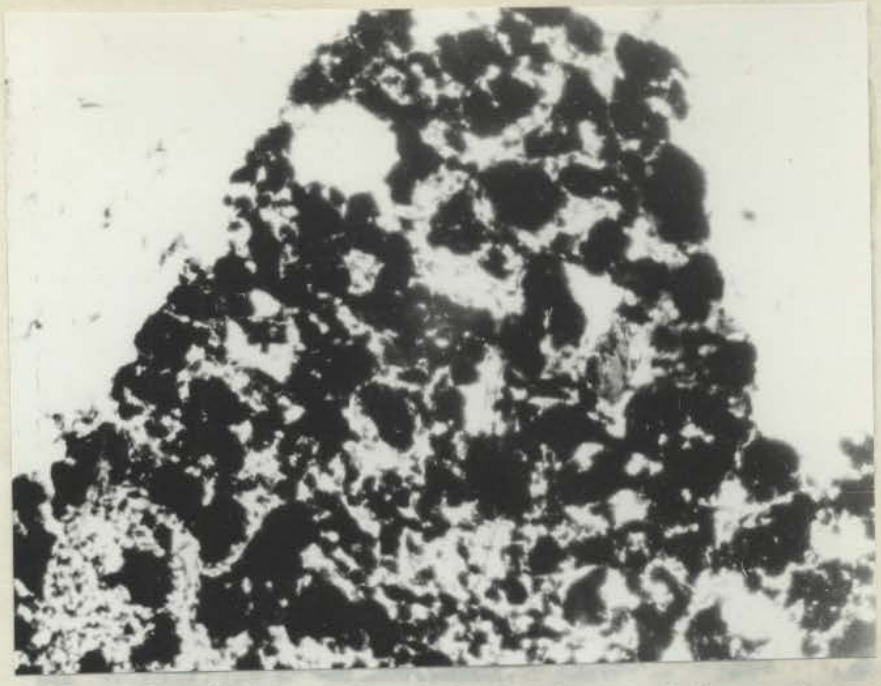

Fig. 35. Bituminous coal. Rat 360 days. Intraperitoneal Injection. 100x. Showing portion of nodule in omentum. Observe absence of fibrosis, round cell infiltration and degenerative changes.

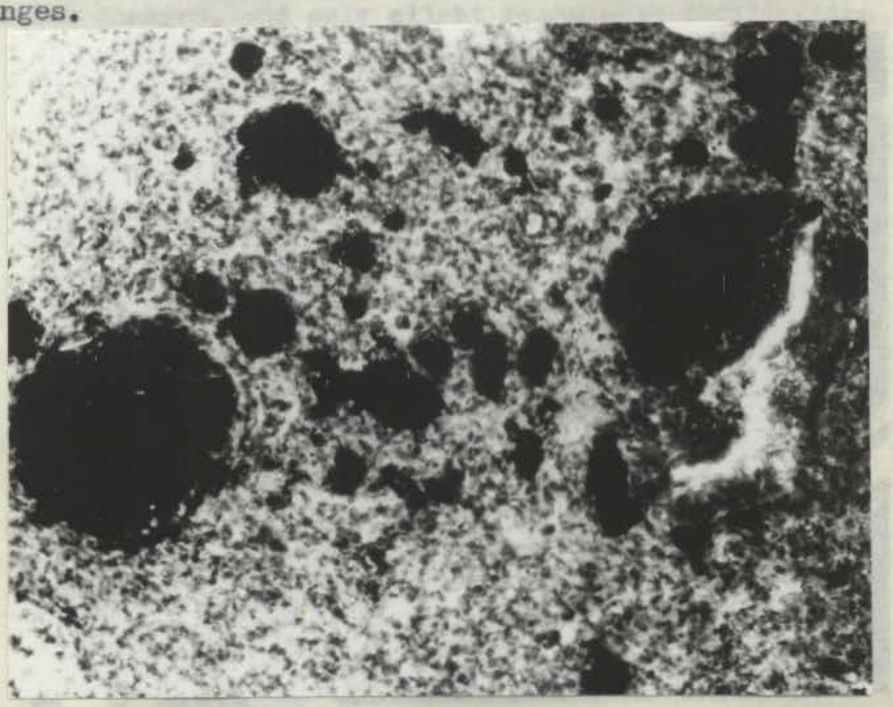

Fig. 36. Hematite. Rabbit 7 months. Lung. 100x Showing aggregations of hematite in lung. Notice absence of round cell infiltration, fibrosis, and degenerative changes in and about nodules. Rabbit died of pneumonia.

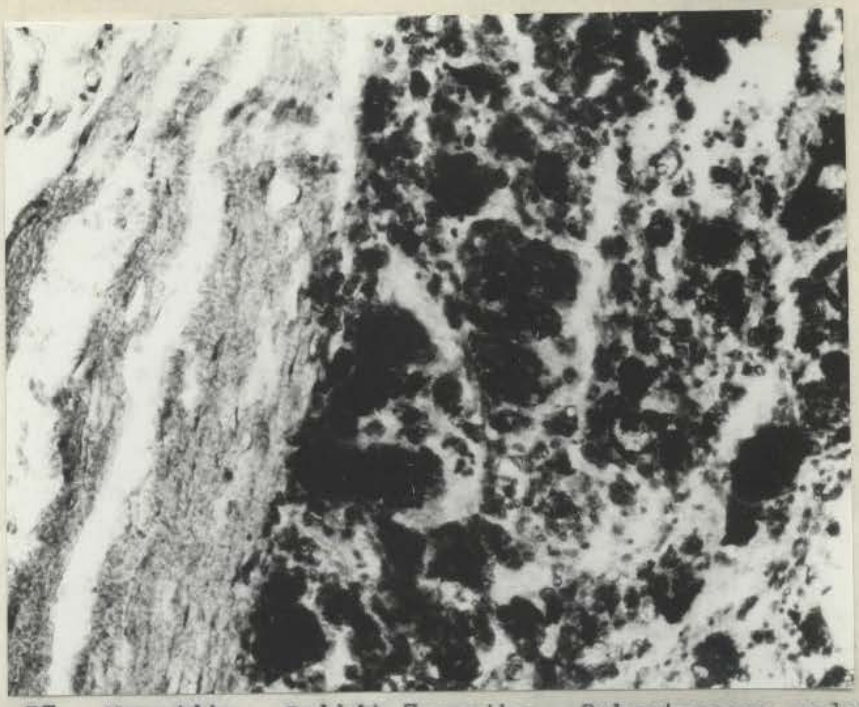

Fig. 37. Hematite. Rabbit 7 months. Subcutaneous nodule. 100x. Portion of the nodule showing thin capsule and aggregations of dust phagocytes. Observe lack of fibrosis, degenerative changes, and only slight round cell infiltration.

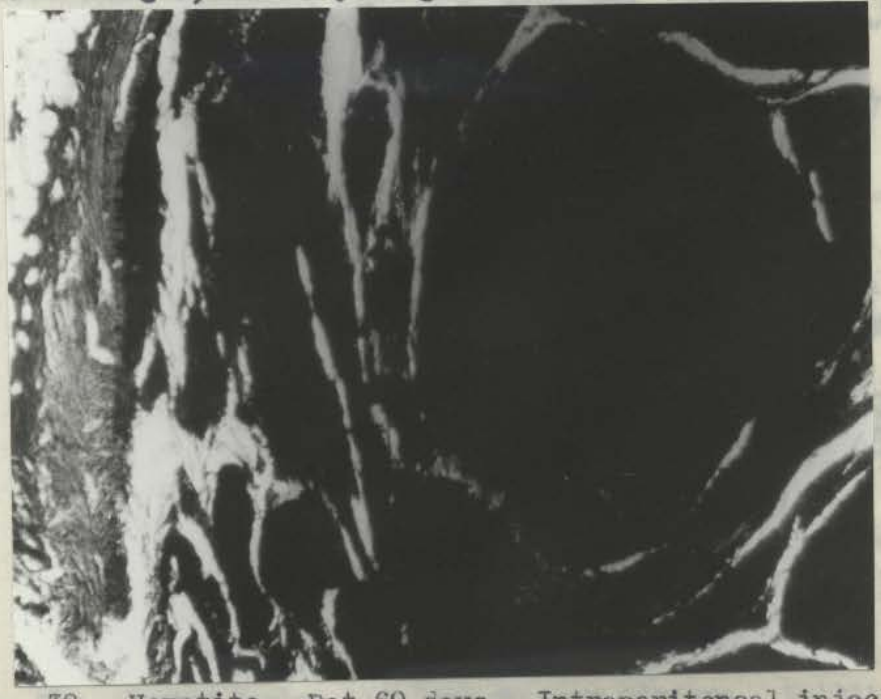

Fig. 38. Hematite. Rat 60 days. Intraperitoneal injection. 40x. Portion of nodule on ventral abdominal wall. Observe uniformity in dust distribution, and lack of round cell infiltration, fibrosis, and degenerative changes.

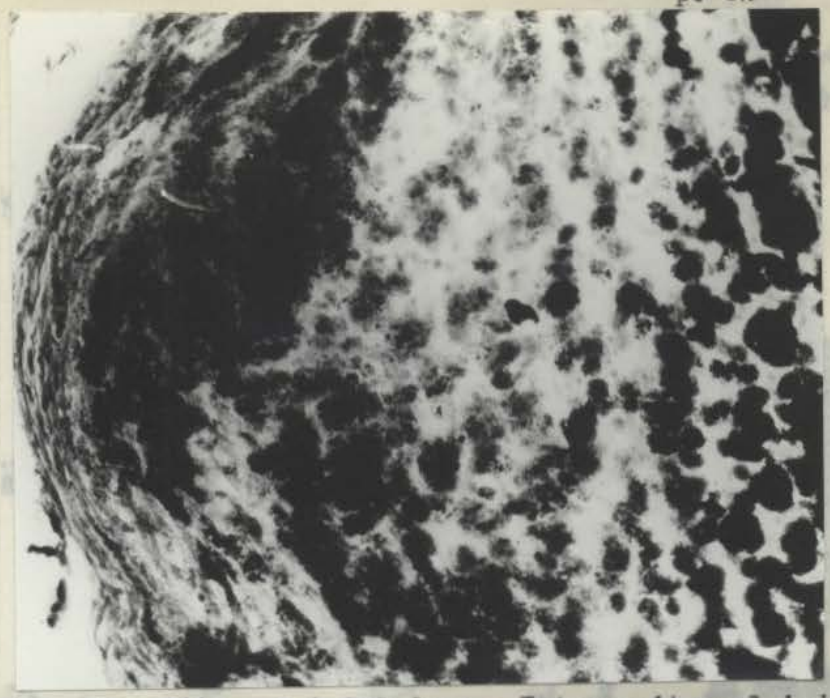

Fig. 39. Hematite. Rat 200 days. Intraperitoneal injection. 100x. Portion of nodule on ventral abdominal wall. Observe large amount of dust in phagocytes and absence of round cell infiltration, fibrosis, or degenerative change.

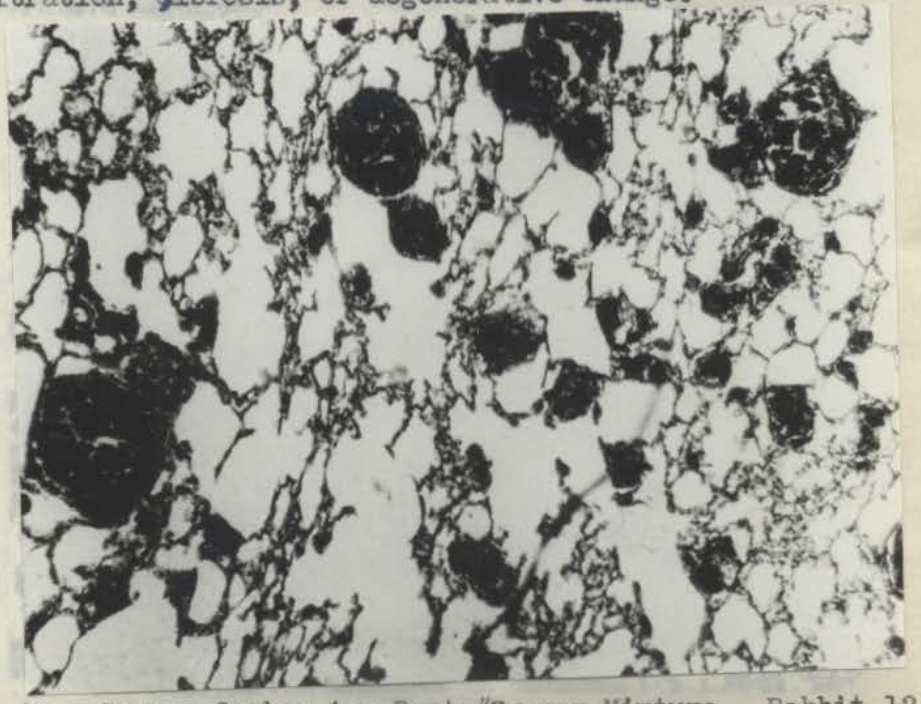

Fig. 40. Suprex Carbon Arc Dust #Suprex Mixture. Rabbit 12 months. Lung. 40x. Showing distribution of dust nodules in parenchyma of lung.

Fig. 41. Suprex Carbon Arc Dust #Suprex Mixture. Rabbit 12 months. Lung. 100x. Showing dust nodules in lung. Observe encapsulation and trabeculation without fibrosis, round cell infiltration, or degenerative changes.

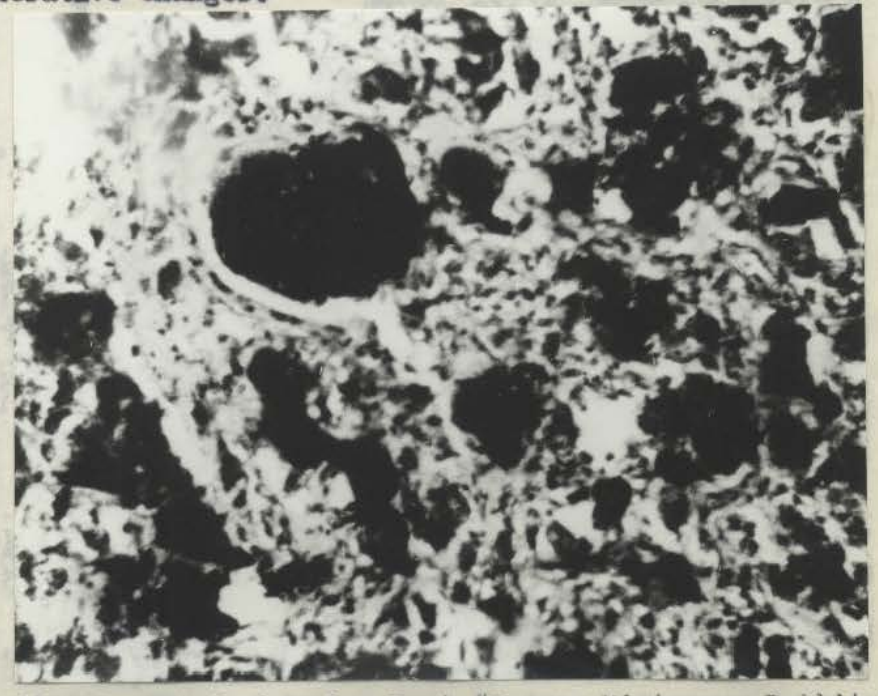

Fig. 42. Suprex Carbon Arc Dust #Suprex Mixture. Rabbit 12 months. 100x. Subcutaneous nodule. Observe aggregates of dust and heavy connective tissue trabeculation. Notice absence of marked fibrosis, round cell infiltration, or degenerative change.

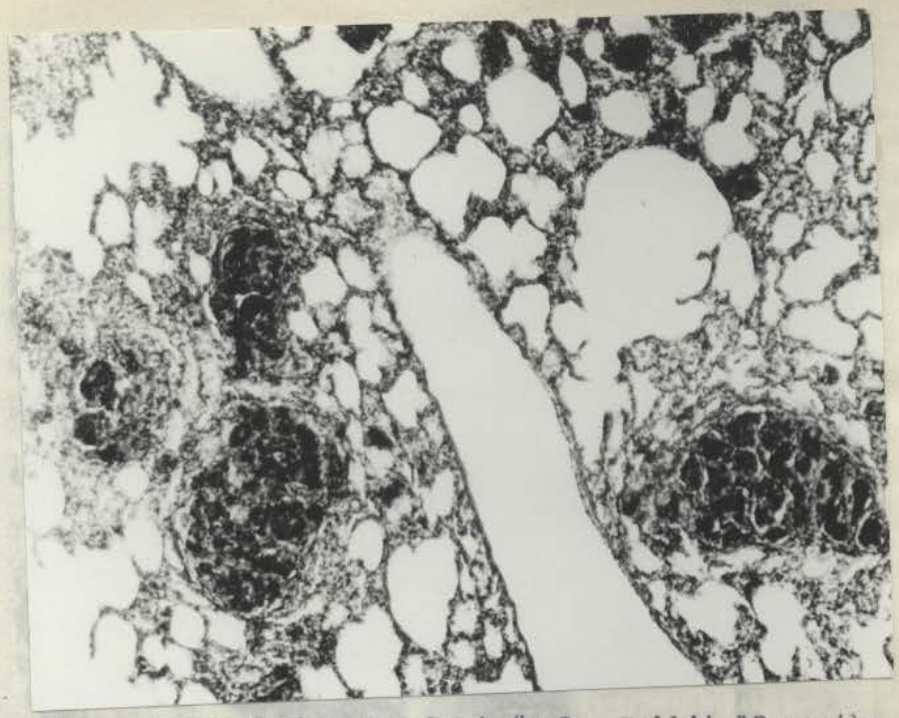

Fig. 43. Suprex Carbon Arc Dust #x-2. Rabbit 12 months. Lung. 40x. Showing distribution of dust nodules in parenchyma of lung.

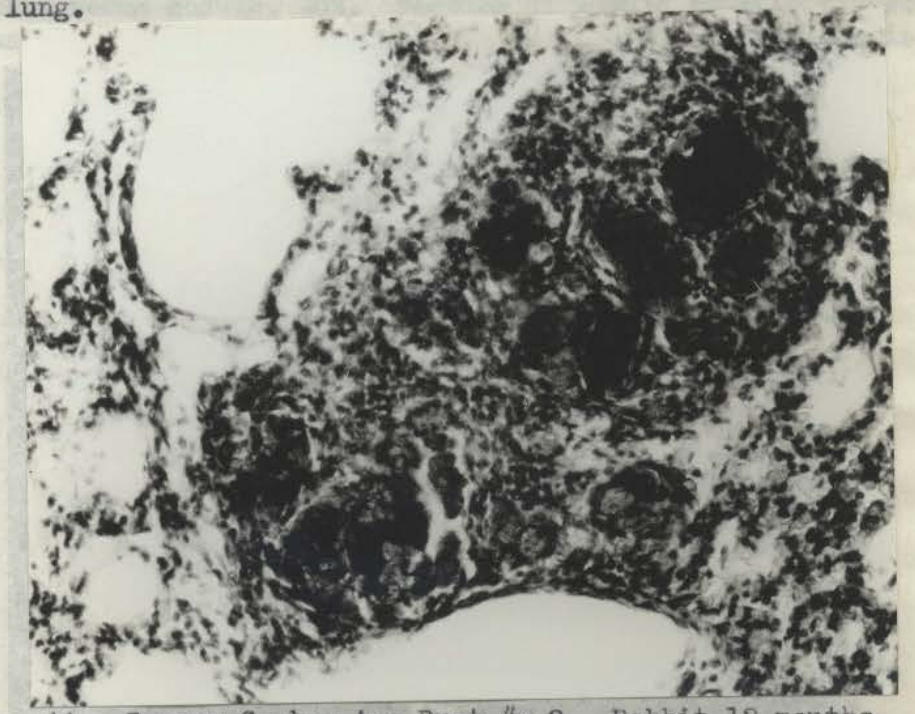

Fig. 44. Suprex Carbon Arc Dust #x-2. Rabbit 12 months. Lung. 100x. Showing dust nodule in lung. Observe encapsulation, slight fibrosis, and round cell infiltration, but absence of degenerative changes.

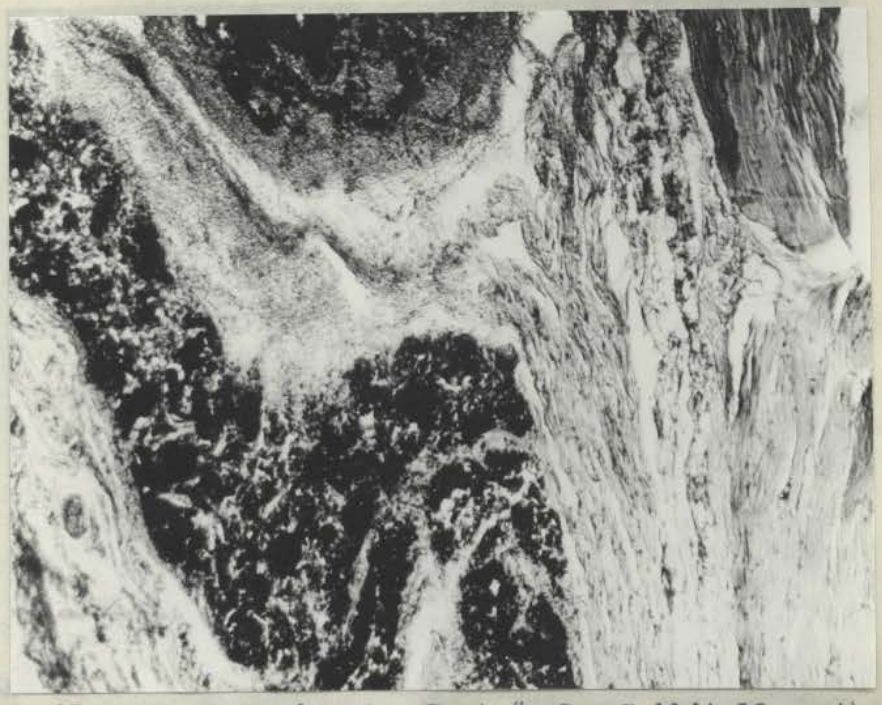

Fig. 45. Suprex Carbon Arc Dust #x-2. Rabbit 12 months. Subcutaneous nodule. 40x. Portion of nodule showing connective tissue trabeculation, but absence of proliferative fibrosis.

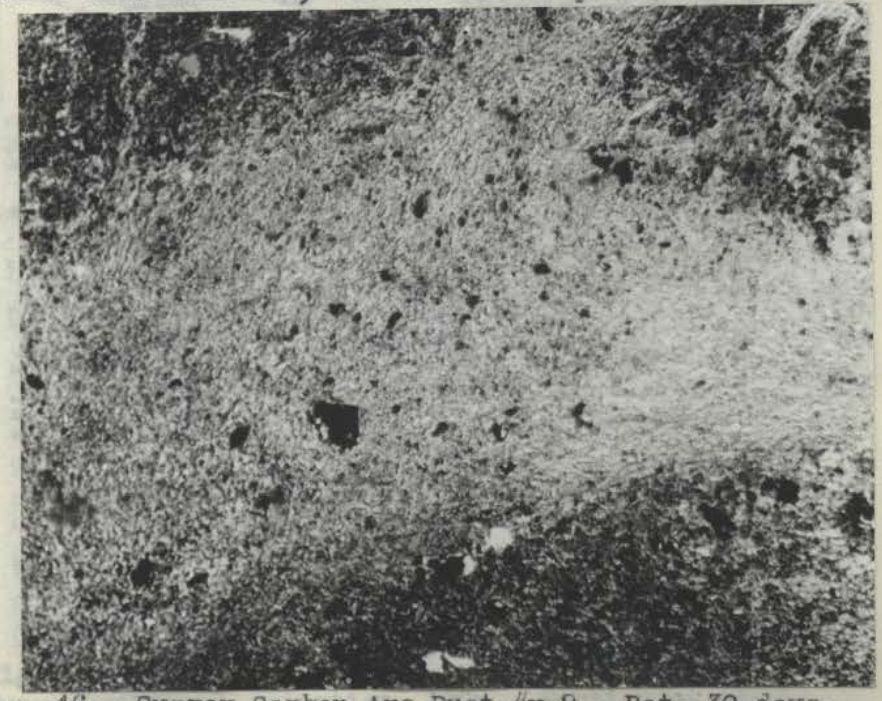

Fig. 46. Suprex Carbon Arc Dust #x-2. Rat. 30 days. Intraperitoneal injection. 40x. Portion of omental nodule. Observe proliferative fibrosis and density of tissue.

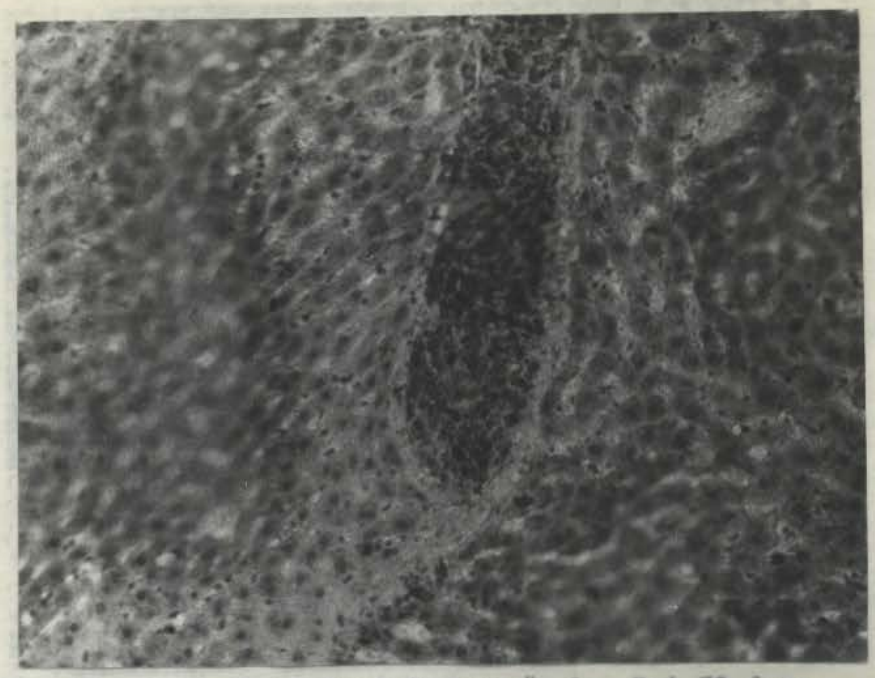

Fig. 47. Carbon Arc Dust Suprex #x-2. Rat 30 days. Intraperitoneal injection. 100x. Liver: Observe dust nodule in connective tissue trabeculae of the liver.

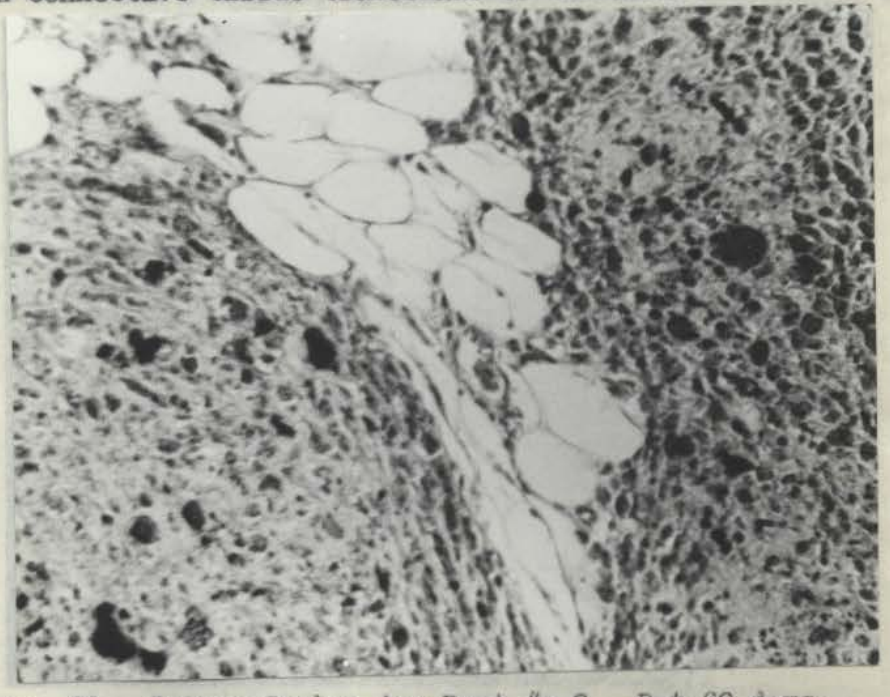

Fig. 48. Suprex Carbon Arc Dust #x-2. Rat 60 days. Intraperitoneal injection. 100x. Portion of omental nodule. Observe proliferative fibrosis and density of tissue.

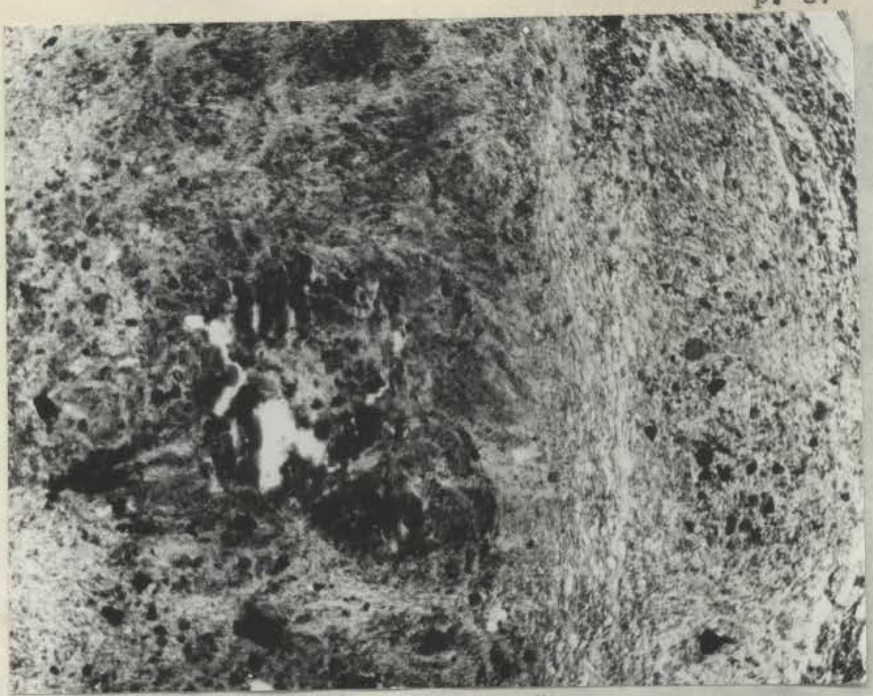

Fig. 49. Suprex Carbon Arc Dust #x-2. Rat 60 days.
Intraperitoneal injection. 40x. Portion of omental nodule.
Note marked fibrosis, hyaline degeneration, and tissue necrosis.

Fig. 50. Suprex Carbon Arc Dust #x-2. Rat 90 days.
Intraperitoneal Injection. 40x. Portion of omental nodule.
Note marked fibrosis, hyaline degeneration, and tissue necrosis.

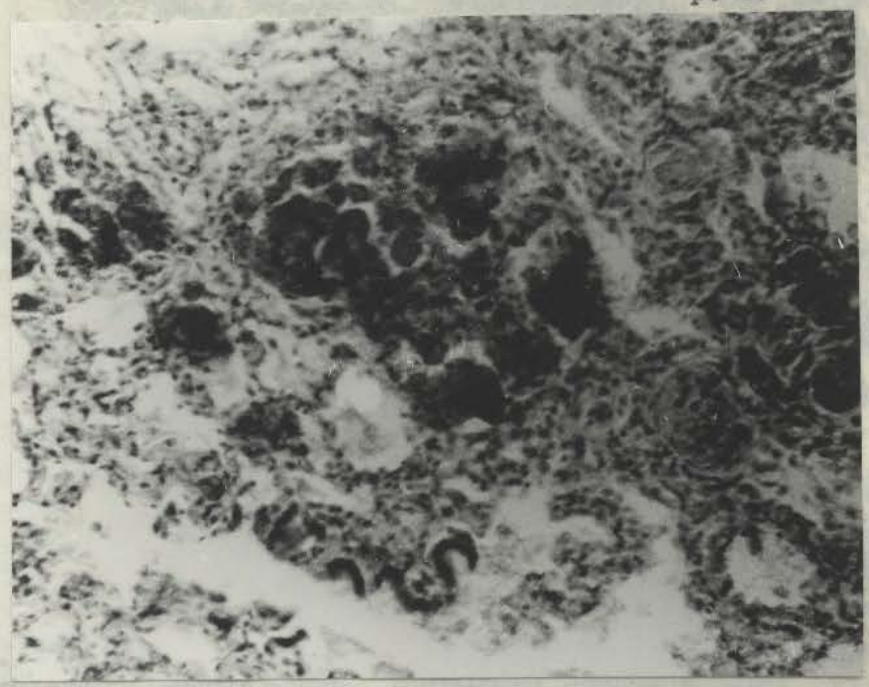

Fig. 51. Suprex Carbon Arc Dust #5643. Rabbit 12 months. Lung. 100x. Showing dust nodules in lung. Observe encapsulation, but absence of marked fibrosis, round cell infiltration, or degenerative change.

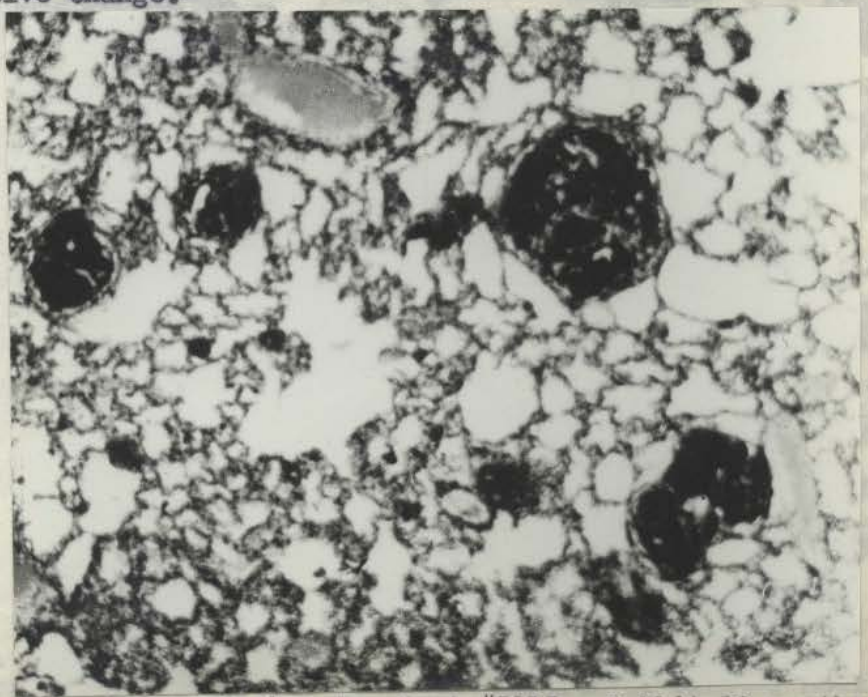

Fig. 52. Suprex Carbon Arc Dust #5913. Rabbit 12 months. Lung. 40x. Showing distribution of dust nodules in the lung.

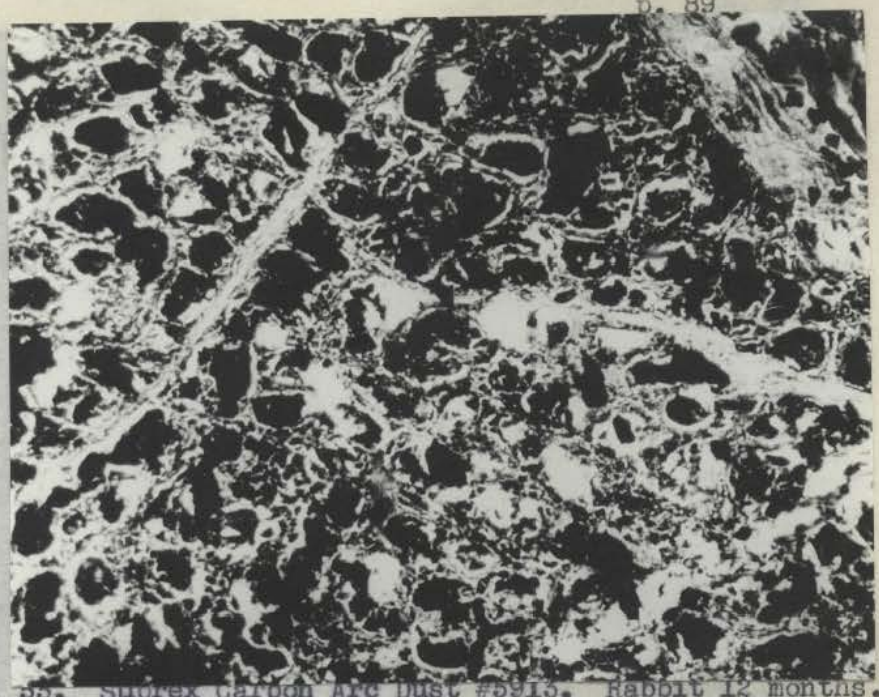

Fig. 53. Suprex Carbon Arc Dust #5913. Rabbit 12 months. Subcutaneous nodule. 40x. Portion of nodule showing connective tissue trabeculation, but absence of fibrosis or degenerative change.

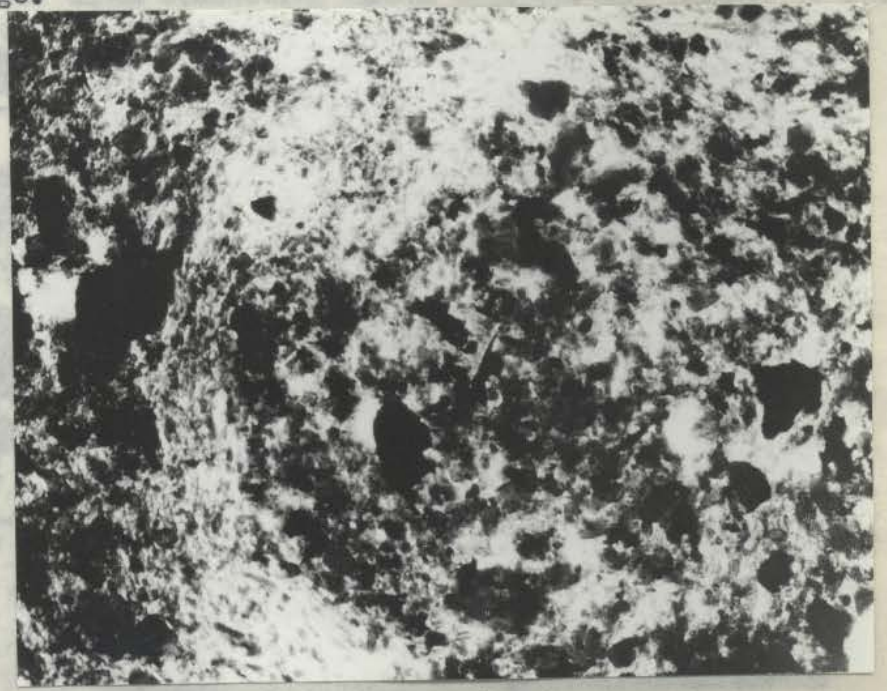

Fig. 54. Suprex Carbon Arc Dust #5913. Rat 30 days. Intraperitoneal injection. 100x. Portion of omental nodule. Observe mild fibrosis, but absence of round cell infiltration, or degenerative change.

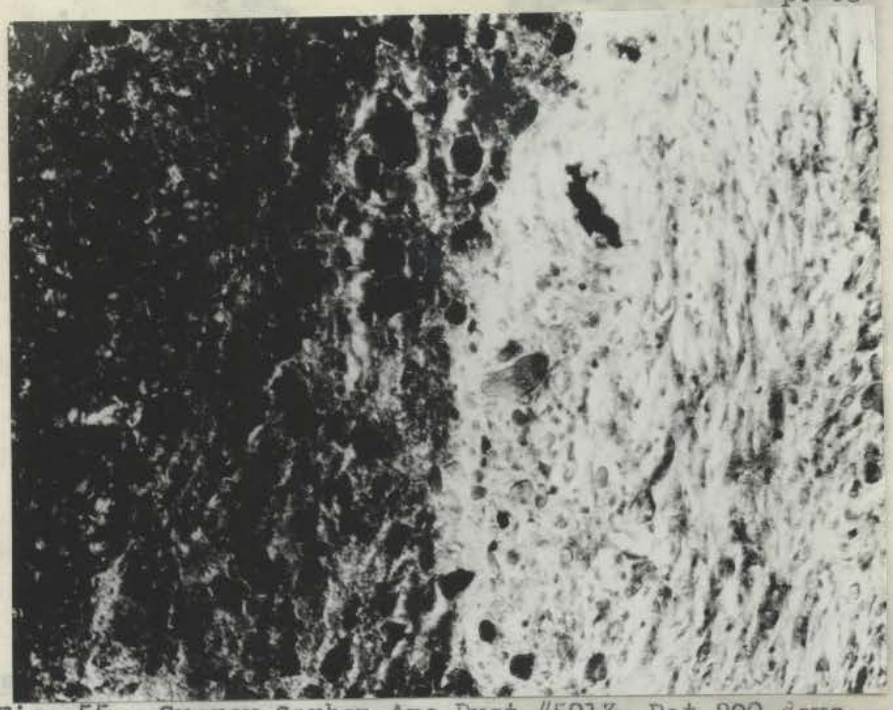

Fig. 55. Suprex Carbon Arc Dust #5913. Rat 200 days. Intraperitoneal injection. 100x. Portion of omental nodule. Observe thick connective tissue capsule, but absence of progressive fibrosis, found cell infiltration, or degenerative change.

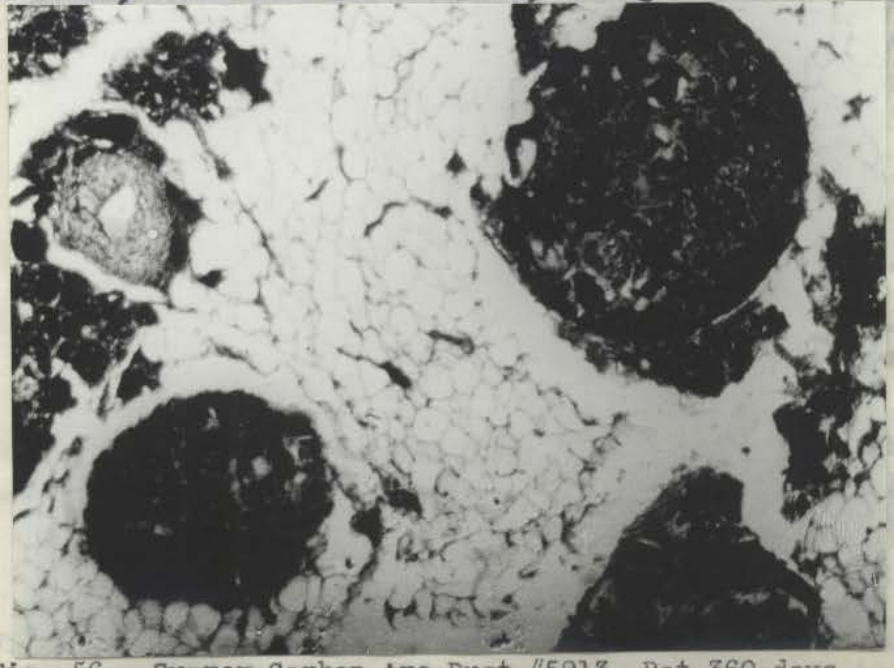

Fig. 56. Suprex Carbon Arc Dust #5913. Rat 360 days. Intraperitoneal injection. 40x. Omental nodules. Observe lack of stratified structure of nodule.

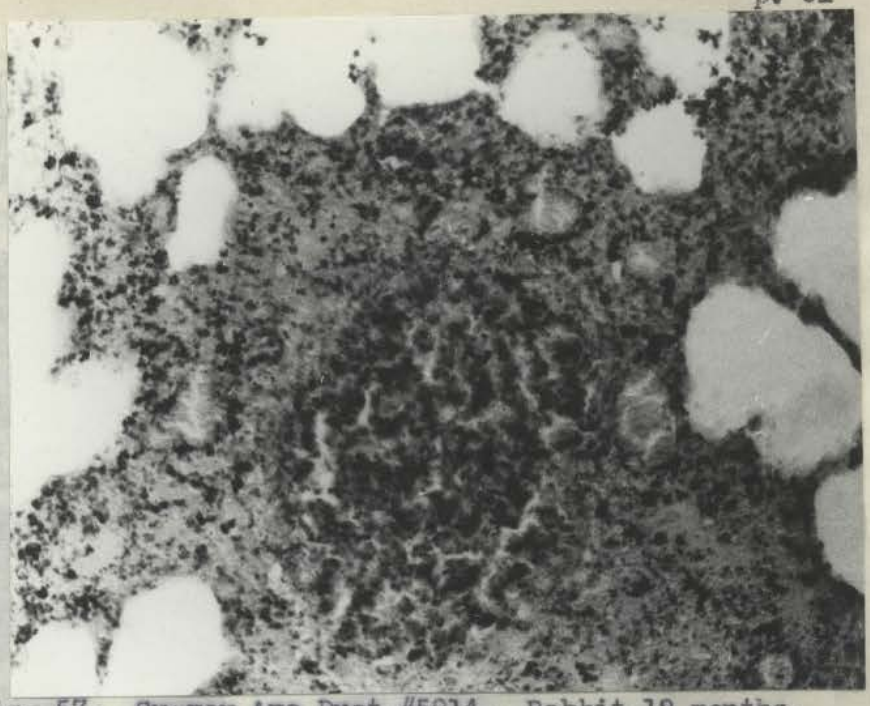

Fig. 57. Suprex Arc Dust #5914. Rabbit 12 months. Intratracheal injection into lung. 100x. Showing dust nodule in lung. Observe only slight tendency to encapsulation and absence of marked round cell infiltration or degenerative change.

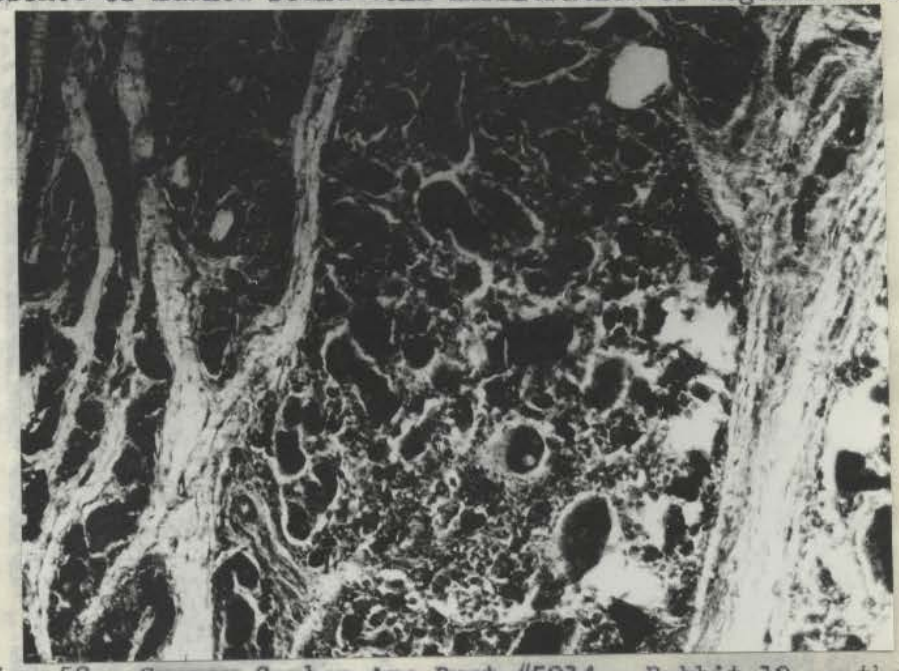

Fig. 58. Suprex Carbon Arc Dust #5914. Rabbit 12 months. Subcutaneous injection. 100x. Portion of nodule showing lack of marked fibrosis and alck of round cell infiltration or degenerative changes.

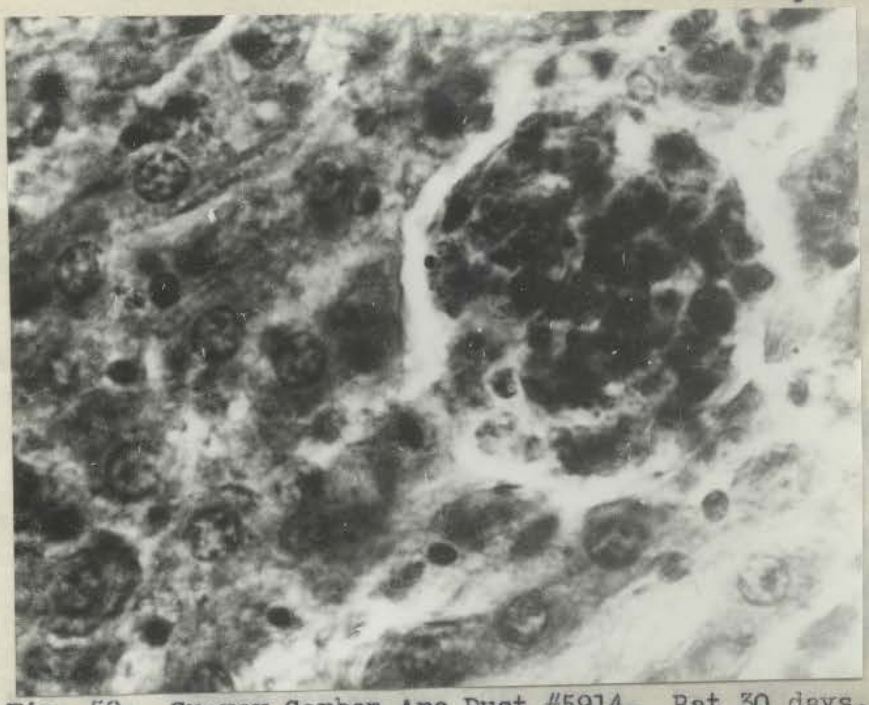

Fig. 59. Suprex Carbon Arc Dust #5914. Rat 30 days. Intraperitoneal injection. 440x. Liver: Showing dust nodules in liver tissue. Nodules are in periportal positions.

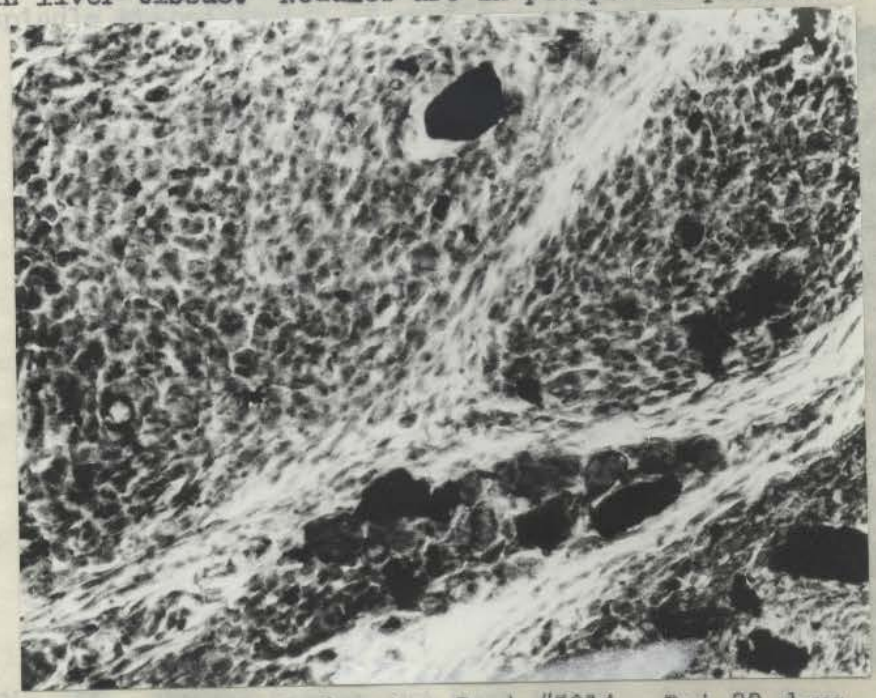

Fig. 60. Suprex Carbon Arc Dust #5914. Rat 90 days. Intraperitoneal injection. 100x. Portion of omental nodule. Note proliferative fibrosis.

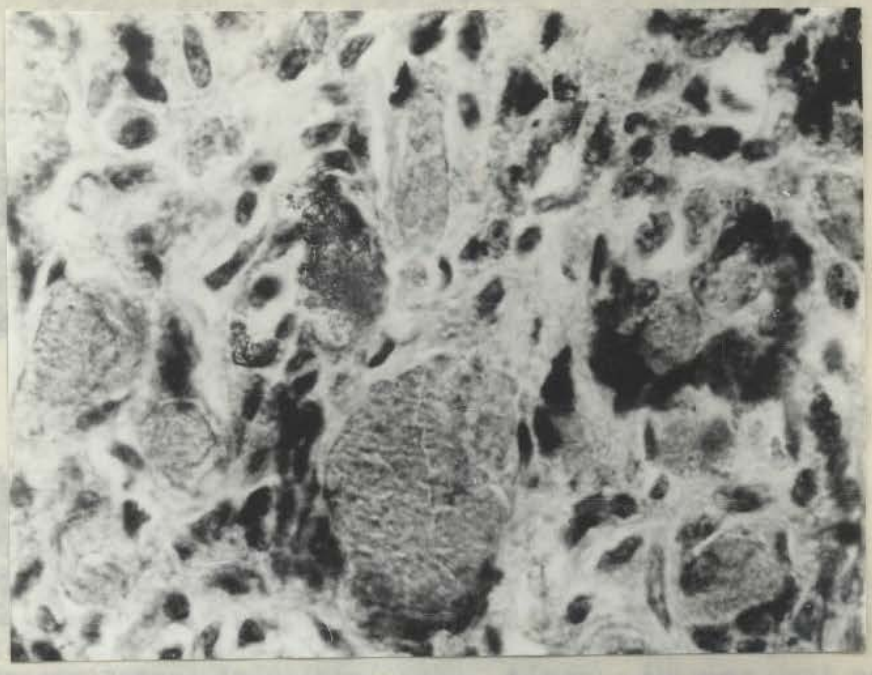

Fig. 61. Suprex Carbon Arc Dust #5914. Rat 360 days. Intraperitoneal injection. 440x. Portion of omental nodule. Note large dust phagocytes filled with dust particles. Observe spindle shaped nuclei of proliferating fibrous tissue.

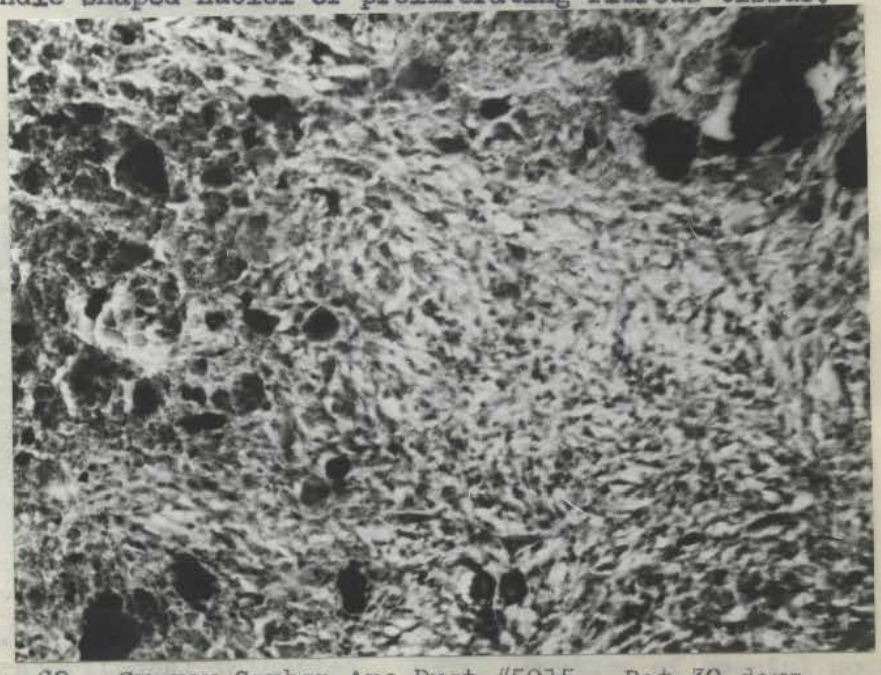

Fig. 62. Suprex Carbon Arc Dust #5915. Rat 30 days. Intraperitoneal injection. 100x. Portion of omental nodule. Observe dense fibrosis.

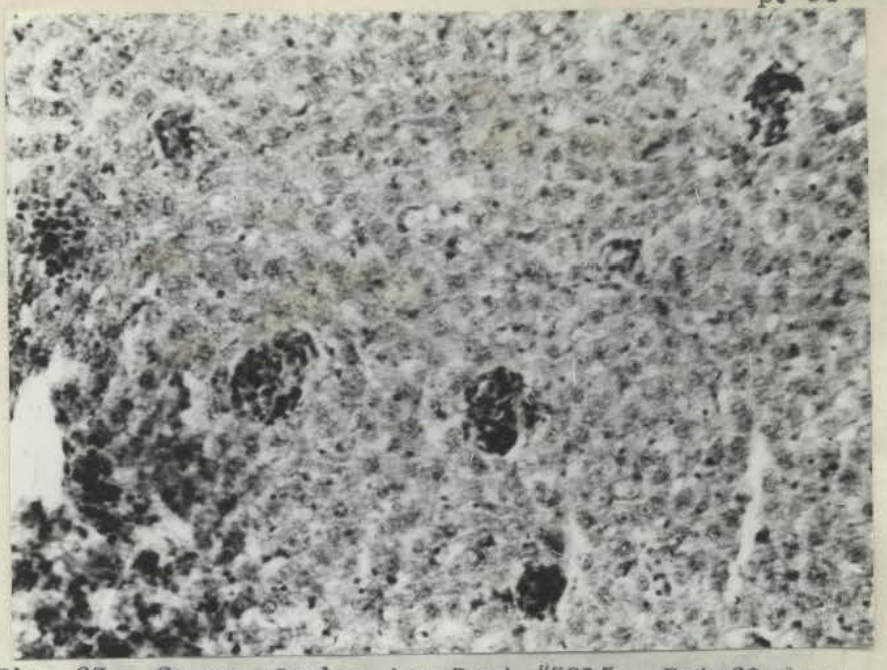

Fig. 63. Suprex Carbon Arc Dust #5915. Rat 60 days. Intraperitoneal injection. 100x. Liver: Showing dust nodule in parenchyma.

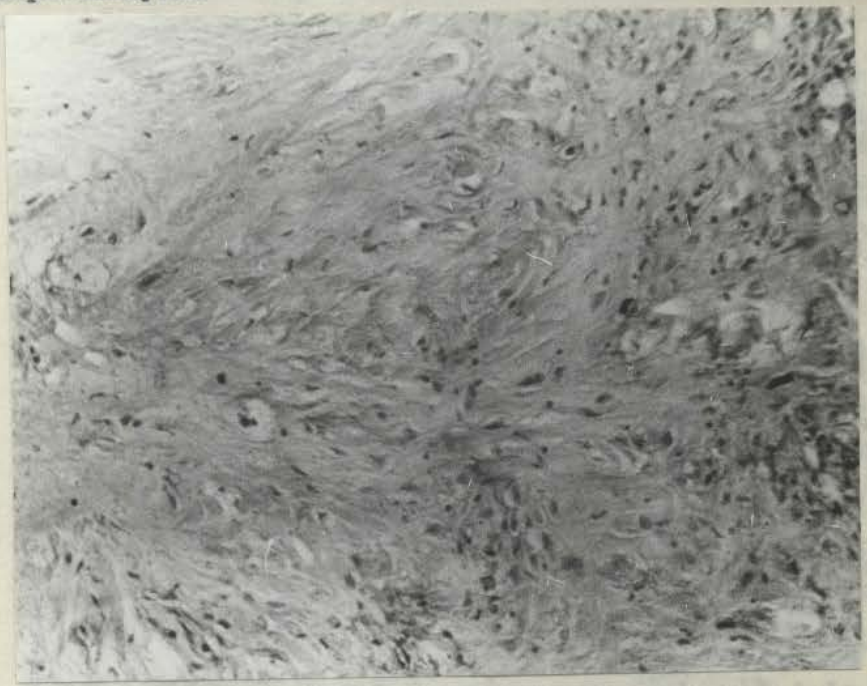

Fig. 64. Suprex Carbon Arc Dust #5915. Rat 60 days. Intraperitoneal injection. 100x. Portion of omental nodule. Observe fibrosis and hyaline degeneration of the tissue.

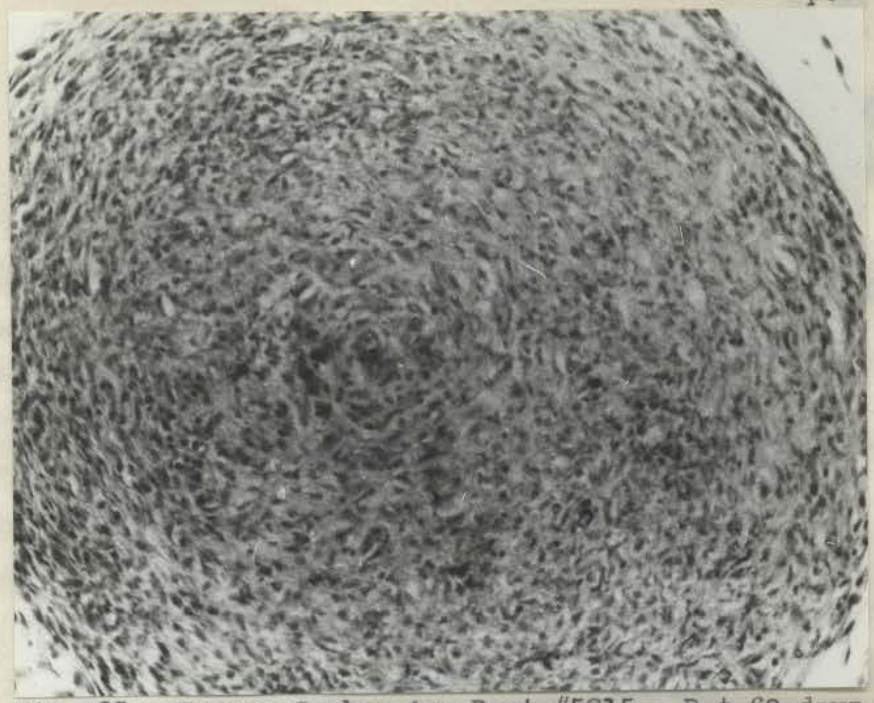

Fig. 65. Suprex Carbon Arc Dust #5915. Rat 60 days. Intraperitoneal injection. 100x. Omental nodule showing stratified appearance and marked fibrosis.

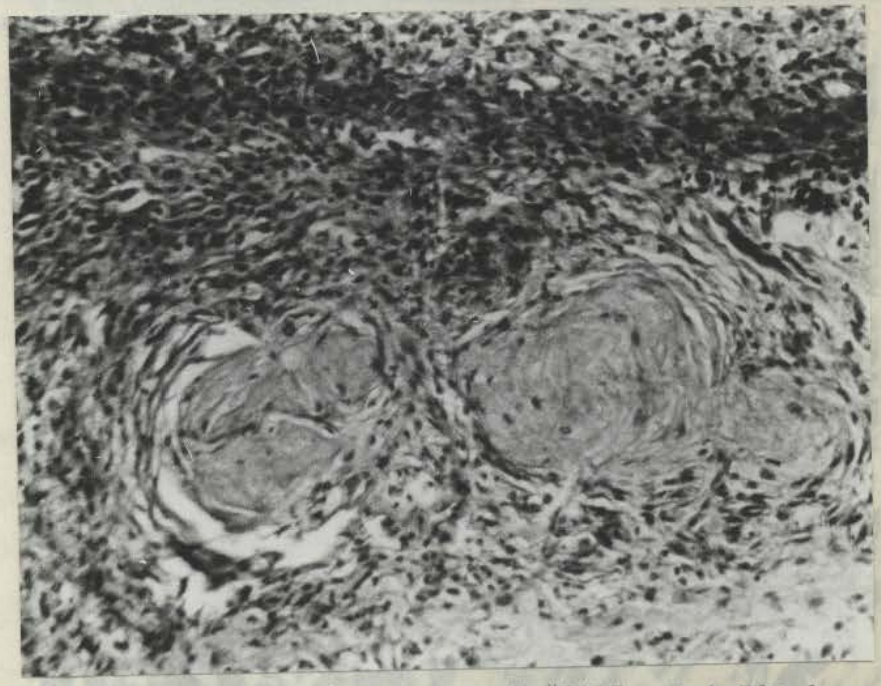

Fig. 66. Suprex Carbon Arc Dust #5915. Rat 360 days. Intraperitoneal injection. 100x. Portion of omental nodule. Note marked fibrosis, and hyaline degeneration of tissue.

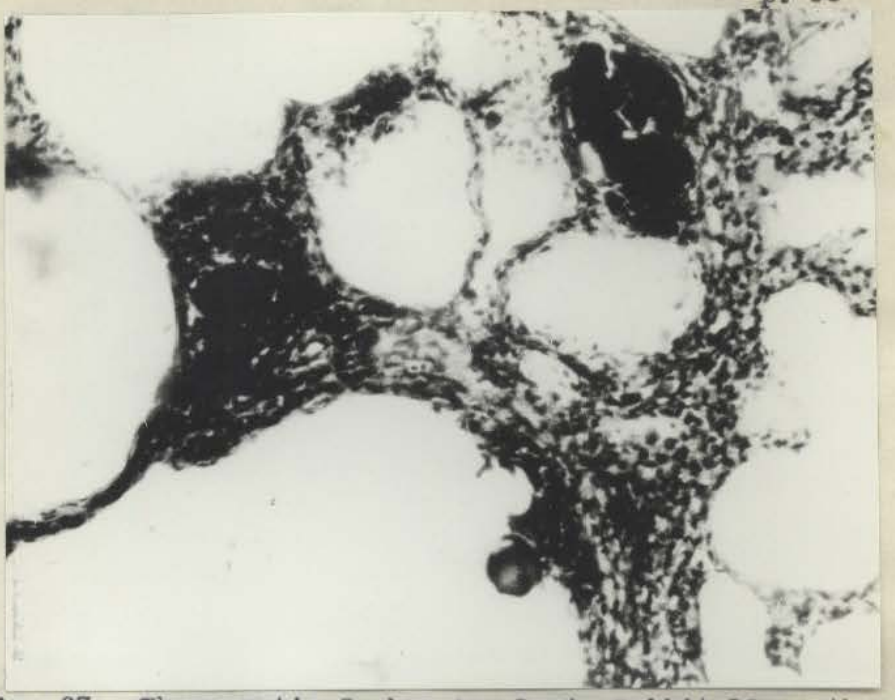

Fig. 67. Therapeutic Carbon Arc Dust. Rabbit 12 months. Lung. 100x. Showing dust nodule in lung. Notice fine encapsulation and absence of fibrosis, round cell infiltration, or degenerative change.

Fig. 68. Therapeutic Carbon Arc Dust. Rabbit 12 months. Subcutaneous nodule. 100x. Note absence of fibrosis, round cell infiltration, or degenerative change.

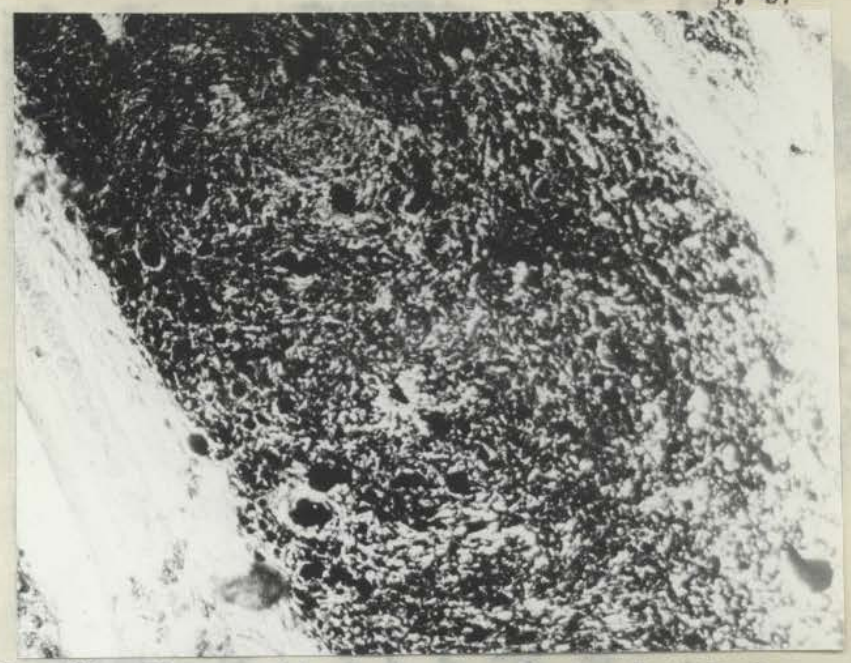

Fig. 69. Therapeutic Carbon Arc Dust. Rat 90 days. Intraperitoneal injection. 40x. Portion of omental nodule. Note only slight fibrosis, and absence of degenerative change.

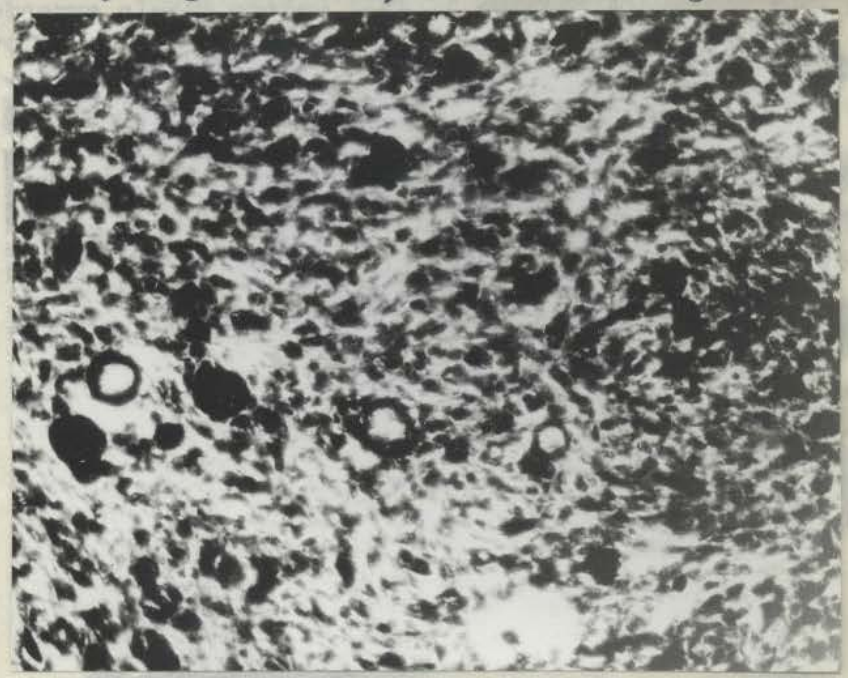

Fig. 70. Therapeutic Carbon Arc Dust. Rat 90 days. Intraperitoneal injection. 100x. Portion of omental nodule. Note absence of marked fibrosis, round cell infiltration, or degenerative change.

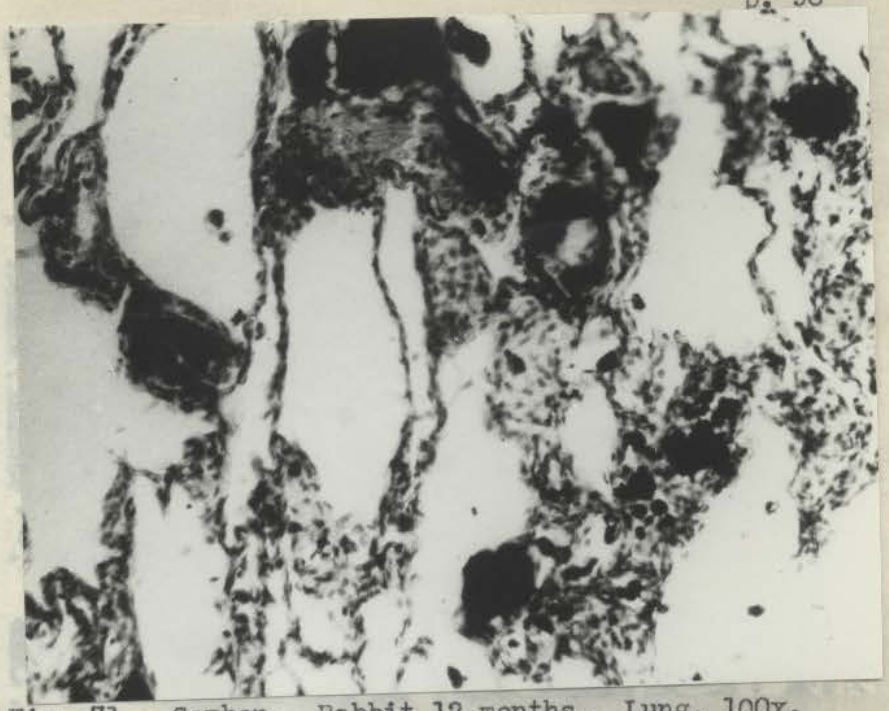

Fig. 71. Carbon. Rabbit 12 months. Lung. 100x.
Showing distribution of aggregations of dust cells in the lung. Observe almost entire lack of encapsulation and lack of fibrosis, round cell infiltration, or degenerative change.

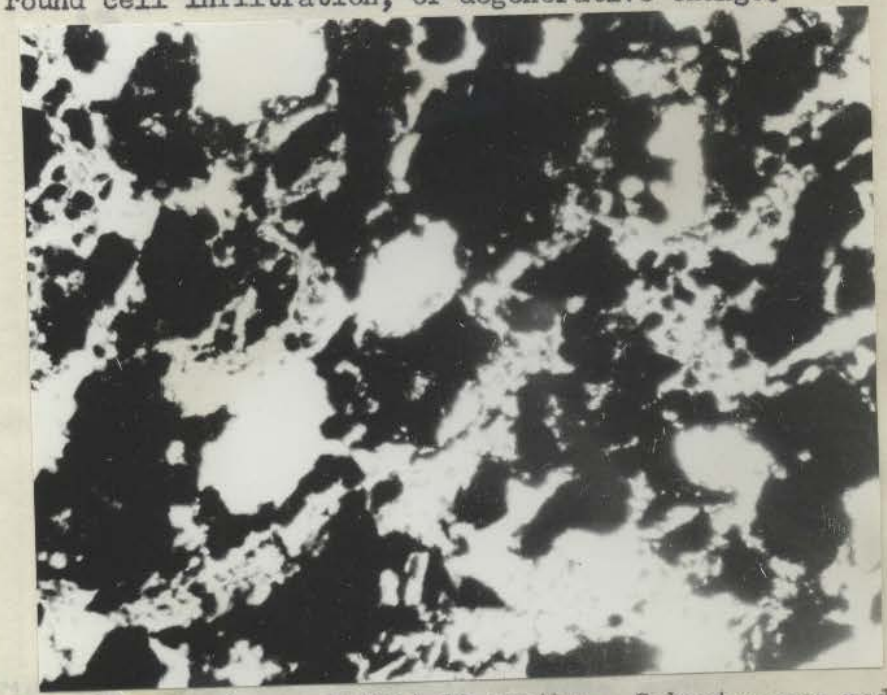

Fig. 72. Carbon. Rabbit 12 months. Subcutaneous nodule. 100x. Portion of the nodule showing aggregates of dust and dust phagocytes and lack of fibrosis, round cell infiltration, or degenerative change.

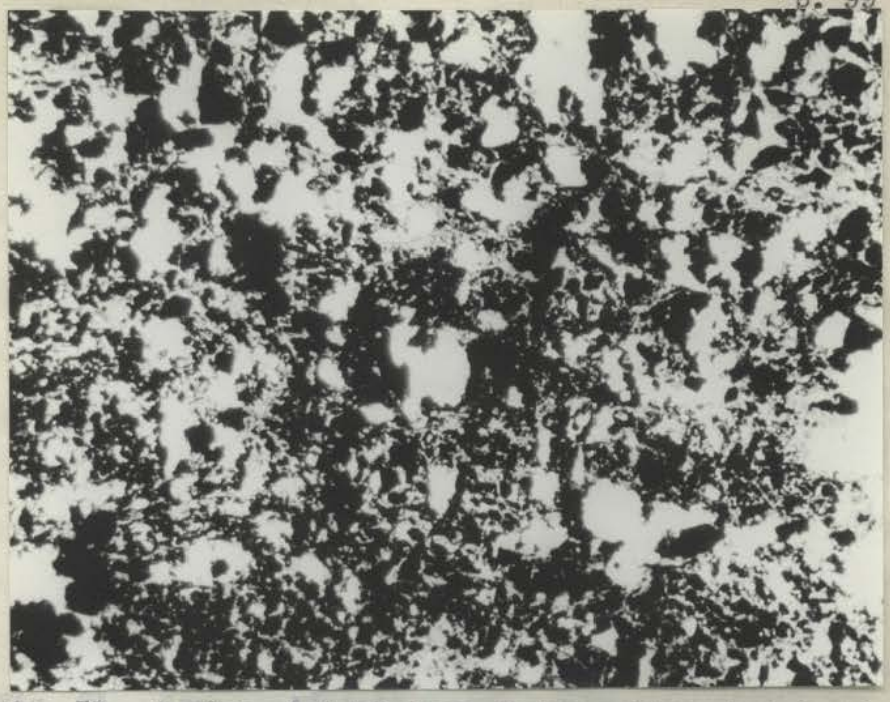

Fig. 73. Carbon. Rat 60 days. Intraperitoneal injection. 100x. Portion of omental nodule showing absence of fibrosis, found cell infiltration, or degenerative change.

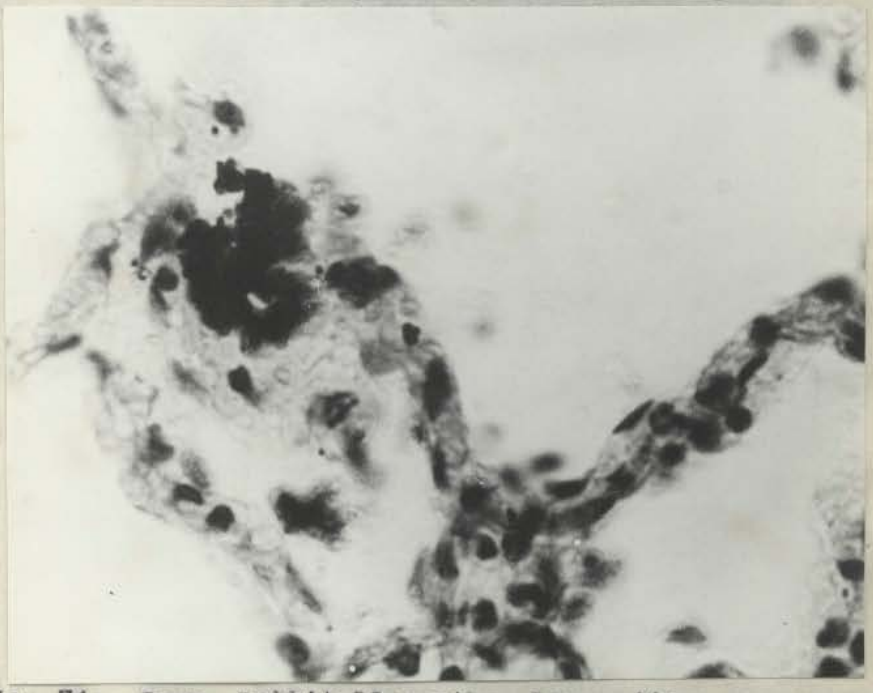

Fig. 74. Core. Rabbit 12 months. Lung. 440x.
Lung showing aggregation of dust in alveolar wall. Notice absence of encapsulation, fibrosis, round cell infiltration or degenerative changes.

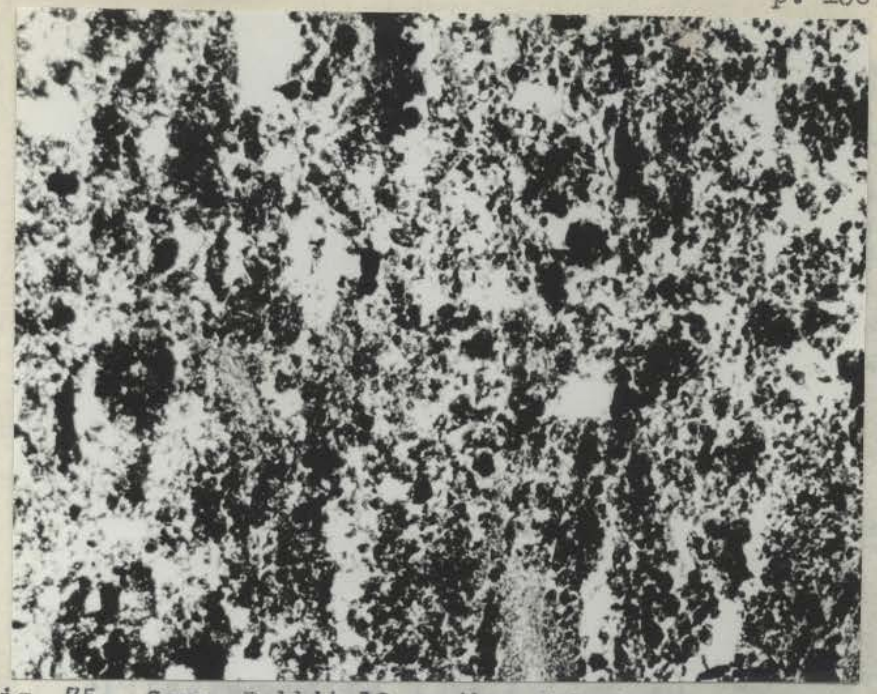

Fig. 75. Core. Rabbit 12 months. Subcutaneous nodule. 40x. Portion of subcutaneous nodule showing lack of fibrosis and degenerative changes.

Fig. 76. Core. Rat 60 days. Intraperitoneal injection. 40x Portion of omental nodule showing only flight fibrosis and absence of degenerative changes.

Fig. 77. Core. Rat 60 days. Intraperitoneal injection. 100x. Portion of nodule on ventral abdominal wall. Observe mild fibrosis and absence of round cell infiltration or degenerative change.

Photographic Supplement