

een studied in more detail. In general, delay in onset of from 2 to 60 days following whether the result of a single large dose or doses.

s have been observed qualitatively, good are lacking, particularly in regard to

riely obvious that animals can be injured by segment of the electromagnetic spectrum; that humans are similarly affected. Further being done. The important problems are re-evaluation of exposure; limits of exposure and power; continuing studies of humans; hazard is indicated, the question of methods investigated. In the meantime it is strongly to microwaves, particularly from radar protection is particularly important. Some use of special screen glasses for this any problems involved in their use.

b discussion will stimulate sufficient interest that answers will be found which will it as no problem, or if it is a problem, to engineering and medical—for controlling it.

RECENT OBSERVATIONS ON CHRONIC PULMONARY BERYLLIUM DISEASE

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The concept berylliosis has already become so firmly entrenched in the medical literature that it may seem audacious to challenge its validity. The results obtained from research recently conducted at the Saranac Laboratory¹ impels one, however, to reconsider the criteria of this disease and, more particularly, those pertaining to its chronic manifestations. This research has also brought to light certain interesting aspects of the fundamental pathology of the pulmonary derangements provoked by various compounds of beryllium.

The observations to be briefly presented in this review of the subject are based on the following studies:

- (a) a systematic histological and physico-chemical review of 31 of the 58 lung specimens constituting the Saranac Laboratory collection assembled since 1943 and on which material remained in the Laboratory for detailed study;
- (b) a review of the material and results obtained from the comprehensive series of experiments conducted in the Saranac Laboratory with beryllium compounds since 1943 (Table 1);
- (c) personally conducted long-range experiments on the biological action of a variety of beryllium compounds, acknowledgement being hereby made to the Damon Runyon Fund, American Cancer Society, Atomic Energy Commission and the Office of Naval Research for generous assistance in connection with this work (Table 2);
- (d) a detailed study of the pulmonary material from a current series of nine beryllium pulmonary disease cases; acknowledgement is made for the assistance of physicians who cooperated in furnishing the lung biopsy or autopsy specimens;
- (e) a broad-range investigation of the potential role of beryllium in the genesis of pulmonary diseases not usually associated with the problem of berylliosis (sarcoidosis, anthracosis, asbestosis, siderosis and silicosis).

¹ Acknowledgement is made to O. J. Dobrogorski, M.D.; T. M. Durkan, M.E.; A. B. Delahant; M. Roberts, M.E., and F. Creedon of the Saranac Laboratory for their technical assistance in connection with these programs.

TABLE I.
Beryllium Compounds Tested for their Capacity to Cause Chronic Lesions and Neoplastic Change.
Saranac Laboratory — 1944-1953

BERYLLIUM COMPOUND	ROUTE OF INTRODUCTION						SPECIES OF ANIMALS					
	Venous	Cardiac	Peritoneal	Subcutaneous	Tracheal		Guinea Pigs	Rabbits	Rats	Mice	Swine	Dogs
					Uninfected	Infected						
Beryl.....	O	O	O				O	O	O	O	O	O
Beryllium.....	O	O	O				O	O	O	O	O	O
Be Carbide.....	O	O	O				O	O	O	O	O	O
Be Carbonate.....	O	O	O				O	O	O	O	O	O
Be Hydroxide.....	O	O	O				O	O	O	O	O	O
Be Nitrate.....	O	O	O				O	O	O	O	O	O
Be Oxide.....	O	O	O				O	O	O	O	O	O
Be Phosphate.....	O	O	O				O	O	O	O	O	O
Be Sulphate.....	O	O	O				O	O	O	O	O	O
Be Metal plus B.A.L.....	O	O	O				O	O	O	O	O	O
Be Glass.....	O	O	O				O	O	O	O	O	O
Be Silicate.....	O	O	O				O	O	O	O	O	O
Be Stearate.....	O	O	O				O	O	O	O	O	O
Be Phosphor.....	O	O	O				O	O	O	O	O	O
Be Phosphor plus Alumina	N	O	O				N	N	O	O	O	O

O—Negative capacity to cause chronic lesions
N—Positive capacity to induce bone sarcoma
G—Positive capacity to produce granulomata

Rather obviously it is impossible to get data systematically garnered through experiments, but it has been made instead to certain highlights have topical significance. That new face of interest seems probable, for in the mystery. Furthermore, although a great deal has been applied to the prevention of berylliosis, of new cases have been gratifyingly small, it would seem that the danger has by no means been increasing importance of beryllium in the field of metallurgy points to the possibility that it may yet occur.

Chronic Berylliosis versus Chronic Pulmonary Beryllium Workers

This is the first matter which needs to be considered, the issue appears to be that whether the concept "berylliosis" has been narrowed down to a limited category of cases from exposures to respirable beryllium dust, or whether it is regarded as the essential component of the disease, the question now is whether these non-granulomatous lesions of their own be recognized as pathognomonic of the form of the beryllium disease.

The primary pulmonary manifestations of berylliosis are not present as granulomatous processes, but as chronic bronchitis or a non-specific type of pneumonia. It would not seem illogical, therefore, that berylliosis manifests itself as chronic vasculitis or chronic pneumonitis. In common practice, the diagnosis of the chronic form of the disease is made on the demonstration of granulomata. This requires critical examination. No matter how small the nodular chronic lesions. Asbestos and coal dust analogy is it not possible that too much has been placed on the granuloma as the basis of the beryllium disease and too little on the chronic lesions associated with the inhalation of beryllium dust?

A review of the Saranac Laboratory records revealed that granulomata constituted the basis of about two-thirds of the cases (Figure

TABLE 2.
Beryllium Compounds Tested for Their Capacity to Cause Systemic Derangement
or Fatal or Chronic Lesions or to Provoke Neoplastic Changes.
Period — 1954 and 1955.

BERYLLIUM COMPOUND	ROUTE OF INTRODUCTION						
	Subcutaneous			Inhalation			
	Rats	Rabbits	Swine	Rats	Monkeys	Guinea Pigs	
Beryllium Fluoride.....	+	Δ	+	+	+		
Beryllium Oxide.....	+	Δ	+	G	Δ		
Beryllium Phosphate.....	+	Δ	+	+	+		
Beryllium Sulphate.....	+	Δ	+	N & G	+		
Zn-Be-Mn-Silicate.....	+	Δ	+	N	Δ		Δ
Zn-Be-Mn-Silicate plus A.T.A.	—	Δ	+				
Zn-Be-Mn-Silicate plus Cortisone.....	—	Δ	+				
Zn-Be-Mn-Silicate plus Mg Tungstate.....	—	Δ	+				
BeSO ₄ plus Quartz.....	—	Δ	—	N & G	Δ		
BeSO ₄ plus Fe ₂ O ₃	—	—	—	N & G	Δ		
BeSO ₄ plus Asbestos.....	—	—	—	Δ	Δ		
BeSO ₄ plus Fibreglas.....	—	—	—	Δ	Δ		Δ

Δ—Studies in progress

—Lesions and systemic derangements produced: still under investigation

G—Positive capacity to provoke chronic pulmonary granulomatosis and other lesions

N—Positive capacity to induce pulmonary neoplasia

granulomatosis was either an inconsi-
In the Laboratory we also have a col-
rejected as instances of berylliosis be-
found. Several of these cases had be-
limum-containing aerosols and their lu-
chronic lesions of the kind that accor-
ceptable cases." On chemical or spec-
yielded as much beryllium as was pr-
diagnosis of berylliosis was accepted b-
lomata. The question now arises wheth-
mata should not also be included as ins-
voked pulmonary disease, either becau-
logical phenomena or because of their
the series of cases under review, inter-
infiltration (Figure 2) with or without
reticulosis (Figure 4) constituted a
the cases and was absent in less than
lialization of the alveolar walls and p-
of macrophages of the same kind that
lomata occurred with the same frec
other histological prevalences could be

Suffice it to record at this stage
common feature in chronic beryllium
nificant characteristic of the patholo-
ultimately prove to be a sign of less
panying histo-architectonic changes in
of the latter, perhaps a sign of inad-
fortified in coming to the latter con-
growing body of experimental evid-
almost indistinguishable from those
for berylliosis may be provoked by su-
as well (Figure 6). The granuloma n-
cific manifestation of the reaction to
To make a diagnosis of beryllium dise-
additional histopathological diagnosti-
duction of proof that at least the sp-
beryllium, is also present.

Evidence concerning the range of
which accompany the granulomatous
constitute the chronic beryllium pulm-
possible factors in their genesis, will
this connection reference may be mad-
apparent that at least some of the var-

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TABLE 3.
Dispersion of Dominant Histological Features in 40 Cases
of Chronic Pulmonary Beryllium Disease.

Tissue Reaction	None	Slight	Moderate	Severe	Excessive	Universal
GRANULOMATA						
Macrophage Core.....	2	2	15	14	5	2
Plasma Cell Cortex.....	6	20	9	5	2	0
Giant Cells.....	5	12	12	7	4	0
Peripheral Collagen.....	4	11	11	8	4	2
Interstitial Collagen.....	7	15	10	6	2	0
Peripheral Reticulum.....	4	7	14	9	3	0
Central Reticulum.....	5	14	10	8	3	0
ALVEOLAR WALL LESIONS						
Macrophage Invasion.....	3	5	13	9	7	3
Collagenosis.....	4	13	10	7	6	4
Reticulosis.....	0	11	14	15	0	0
Elastic Destruction.....	3	5	9	12	7	4
Ischaemia.....	8	17	11	4	0	0
Epithelialization.....	10	7	9	8	3	2
ALVEOLAR SPACE CHANGES						
Macrophages.....	2	6	13	10	7	2
Foamy Cells.....	9	18	9	3	2	0
Organizing Exudate.....	28	6	4	2	0	0
Focal Atelectasis.....	4	7	11	10	8	0
Atrophic Emphysema.....	6	10	12	6	4	2
FOREIGN BODIES						
Conchoids.....	19	8	5	3	3	3
Crystal Clefts.....	21	8	5	4	2	0
Pigment.....	28	6	4	2	0	0
VASCULAR DAMAGE						
Peri-arterial Fibrosis.....	1	4	20	9	6	0
Pericapillary Collagen.....	5	12	10	5	8	0
BRONCHIAL DAMAGE						
Peribronchial Reaction.....	4	16	15	4	1	0
Endobronchial Reaction.....	17	15	7	1	0	0

The numbers given in the table are the numbers of cases showing various grades of tissue reaction.

beryllium disease may be ascribable to etio beryllium itself or to differences in the form in which the beryllium is introduced also on the dosage, on the speed with which it occurs, on the presence of associated diseases, on the enigmatic factors concerned in individual susceptibility. It is probable that the granuloma only arises when certain factors are present so that the true nature of the disease may be a non-granulomatous process.

On the experimental side we have shown that chronic beryllium disease is more complex than has been supposed. Thus we have shown, for instance, that a primary pulmonary necrosis and diffusion of beryllium sulphate has a marked propensity to induce alveolar lining cells with an associated epithelialization of atrophic alveoli. It readily leads to the development of diffuse interstitial disease (figure 7). For long the human chronic disease has been considered as a disease of the alveoli. In animal experiments did not yield abundant granulomata have since been produced but they appear only after prolonged exposure to small amounts of beryllium. The point which has perhaps been not altogether overlooked, may be that the disease duplicated rather precisely many of the changes which regularly accompany human beryllium disease. In view of the animal experimentation it would seem that the animals basically possess the capacity to develop granulomata of macrophages, of plasma cells, and of epithelium, to provoke the deposition of collagen, to provoke the deposition of fibrocytes and to destroy the epithelium. Crystal clefts and conchoidal bodies are also seen in the human disease and so may giant cells be produced by the structure or its altered biochemical composition. These processes may manifest themselves as chronic interstitial collagenoses or as chronic interstitial pneumonitis. The actual degree of resemblance between the human and animal disease is possible to provoke in animals.

Once it be granted that the granuloma is a sufficient criterion of chronic beryllium disease, the additional aforementioned histological features are evidence of beryllium in the diseased tissues.

TABLE 3.
Histological Features in 40 Cases
of Pulmonary Beryllium Disease.

None	Slight	Moderate	Severe	Excessive	Universal
2	2	15	14	5	2
6	20	9	5	2	0
5	12	12	7	4	0
4	11	11	8	4	2
7	15	10	6	2	0
4	7	14	9	3	0
5	14	10	8	3	0
3	5	13	9	7	3
4	13	10	7	6	4
0	11	14	15	0	0
3	5	9	12	7	4
8	17	11	4	0	0
10	7	9	8	3	2
2	6	13	10	7	2
9	18	9	3	2	0
28	6	4	2	0	0
4	7	11	10	8	0
6	10	12	6	4	2
19	8	5	3	3	3
21	8	5	4	2	0
28	6	4	2	0	0
1	4	20	9	6	0
5	12	10	5	8	0
4	16	15	4	1	0
17	15	7	1	0	0

In the table are the numbers of cases showing reaction.

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beryllium disease may be ascribable to etiological agents other than the beryllium itself or to differences in the physical state or chemical form in which the beryllium is introduced into the lung. Much may depend also on the dosage, on the speed with which the tissue reaction occurs, on the presence of associated disease, as well as on numerous enigmatic factors concerned in individual susceptibility. It is strongly probable that the granuloma only arises when such additional etiological factors are present so that the true chronic form of beryllium disease may be a non-granulomatous process.

On the experimental side we have much support for the concept that chronic beryllium disease is more than a mere granulomatosis. Thus we have shown, for instance, that beryllium fluoride provokes a primary pulmonary necrosis and diffuse interstitial fibrosis. Beryllium sulphate has a marked propensity for stimulating the growth of alveolar lining cells with an associated macrophage catarrh and epithelialization of atrophic alveoli. Exposure to beryllium oxide readily leads to the development of diffuse vesicular emphysema. All these substances may also induce the appearance of granulomata (Figure 7). For long the human chronic disease remained suspect because animal experiments did not yield abundant granulomata. Such granulomata have since been produced but they are admittedly scarce and appear only after prolonged exposure to a limited range of compounds. The point which has perhaps been insufficiently stressed, if not altogether overlooked, may be that the animal experimentation duplicated rather precisely many of the histological changes which regularly accompany human beryllium granulomatosis. From a survey of the animal experimentation it would seem that beryllium compounds basically possess the capacity to stimulate the proliferation of macrophages, of plasma cells, and of the alveolar wall lining epithelium, to provoke the deposition of collagen in the absence of fibroblasts or fibrocytes and to destroy the lung elastin and injure endothelium. Crystal clefts and conchoidal bodies apparently are secondary phenomena and so may giant cells be a reaction to altered tissue structure or its altered biochemical composition. These fundamental processes may manifest themselves as granulomata or may present as chronic interstitial collagenoses or even as an alveolar catarrh. The actual degree of resemblance between the variations of the disease in man match rather closely the nuances of reaction which it has been possible to provoke in animals.

Once it be granted that the granuloma may not in isolation be a sufficient criterion of chronic beryllium disease and that either the additional aforementioned histological features or proof of the presence of beryllium in the diseased tissues may be required to establish

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TABLE 4.
Production of Pulmonary Carcinomata in Rats Exposed to Beryllium Sulphate for Six Months and Thereafter Allowed to Survive for Variable Periods Until Sacrificed.

Survival Period Months	Number of Rats Examined	Rats with Carcinomata		Rats with Multiple Carcinomata		Rats with Metastases	
		Number	%	Number	%	Number	%
6 and less	28	6	21.4	—	—	—	—
7—9	20	6	30.0	—	—	—	—
10—12	42	23	54.8	11	26.2	2	4.8
13—18	27	12	44.4	5	18.5	2	7.4
18 and over	14	4	28.6	—	—	1	7.2
Total	131	51	38.9	16	12.2	5	3.8

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an acceptable medico-legal diagnosis, the latter question becomes critically relevant is sufficient?

This question may never be satisfactorily answered because of the paucity of cases suitable for study. The induction period for chronic beryllium disease is the interval between the clinical diagnosis and the final failure to secure an autopsy. Our experience in setting minimal effective dosage levels of record that chronic berylliosis has been reported by physicians not only in the absence of proof but even after chemical studies failed to detect the reasoning being advanced that the disease had previously been present but had since been eradicated by the appropriate biological response. Beryllium disease on the strength of the demonstration of the presence of the element in the affected tissues. It is a medical experience that individuals who have been lightly exposed to beryllium compounds and who while other plant personnel apparently more heavily exposed failed to react. The inverse sense has been invoked to explain these phenomena. In the case of beryllium, however, the degree of pulmonary reaction is a function of dosage and duration of exposure. It is a notable fact that the lungs of human cases of beryllium disease rather frequently contained beryllium. Not all these tissues had previously been examined for beryllium content and perhaps the concept that beryllium exists in the absence of demonstrable quantities from an erroneous assumption that failure to detect beryllium always signified that it had not been found. This is not so.

Beryllium is a natural constituent of the earth's crust (approximately 0.0001% by weight) so that the presence of a lung may not perhaps signify a pathological condition if beryllium is present in amounts above a certain theoretical possibility, admittedly remote. Beryllium, either liberated from atomic or cosmic sources, may find their way into the environment and therefore, arises as to what would constitute a normal level of beryllium in the lung tissue. Reasoning that persons who had spent decades inhaling ear

2. M. Eisenbud - Personal Communication.

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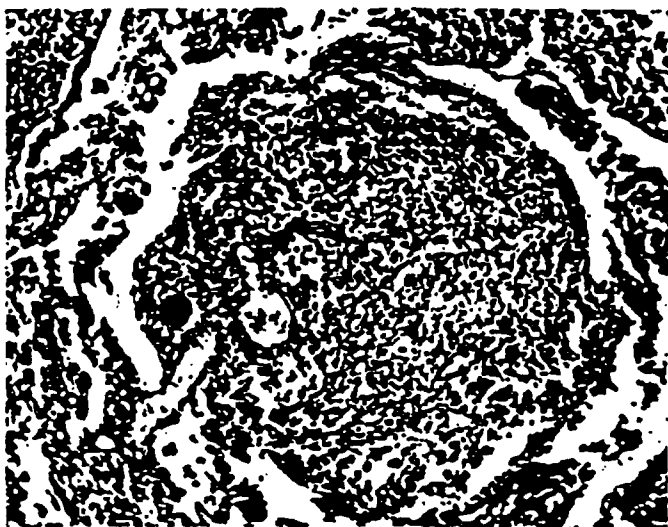


Figure 2.
Diffuse Cellular Infiltration of Alveolar Walls

Figure 1.
Pulmonary Granuloma
Deceased employee of a fluorescent tube manufacturing plant. Exposure to beryllium phosphor. (Mallory - 175 x)

to show the extreme upper limits of contamination in the lung, a review of the accumulated material from various coal fields. The Laboratory was instituted and this additional material from various coal fields contains a relatively high amount of beryllium. These cases have brought to light that coal dusts rather regularly contain a small amount of 0.00 to 0.02% dry tissue with an average of approximately 0.005% dry tissue. We have excluded a number of non-industrial cases of tuberculosis, but have failed to demonstrate beryllium in these cases. Though our inquiry warranted to record that we have found beryllium in persons with a known beryllium exposure, established anthracosis due to coal mining.

The tissues of the coal miners with a as 0.02%/G did not contain any lesions of beryllium industry employees. Berylliosis is a pathological criterion in the absence of any demonstrable amount of beryllium present was the current average for coal miners). The sputum alone, therefore, does not, in the judgment, constitute an adequate factor in the diagnosis. The phenomenon is familiar to those of us who have dealt with silicosis and asbestosis. Thus, in silicosis, which counts, but the proportion of it is of free silica. Similarly the presence of spaces or in the sputum alone does not constitute asbestosis: the asbestos fibrils have to gain entrance where they provoke fibrosis. The asbestos is an epiphenomenon and not the causative factor. The asbestos fibrils which stimulate fibrosis, being the average asbestos body, are usually in the sputum. By analogy we need additional information. In a case of suspected berylliosis, the chemical evidence as a diagnostic criterion is weak. We have x-ray diffraction apparatus and electron microscopy to demonstrate the disease. In cases of beryllium disease it has not yet been determined what form the beryllium compound can take in the genesis of chronic disease. Probably the compounds are essentially inert as human poisons, even perhaps only certain crystal patterns.



Figure 2.
Diffuse Cellular Infiltration of Alveolar Walls
Increased employee of electrical apparatus manu-
facturing industry. Exposure to beryllium com-
pounds (fluorapatite and fluorapatite - 300 x)



Figure 1.
Pulmonary Granuloma
Increased employee of a fluorescent tube
manufacturing plant. Exposure to beryl-
lium phosphor. (Mallory - 176 x)

to show the extreme upper limits of "natural" beryllium concentration in the lung, a review of the accumulated pneumoconiosis cases of the Laboratory was instituted and this series was augmented by additional material from various coal fields, it being known that coal contains a relatively high amount of beryllium. Preliminary study of these cases has brought to light that coal miners' lungs, in particular, rather regularly contain a small amount of beryllium in the range 0.00 to 0.02 γ /G dry tissue with an average beryllium concentration of approximately 0.005 γ /G. We have extended these studies to include a number of non-industrial cases of Boeck's sarcoid and of tuberculosis, but have failed to demonstrate the presence of beryllium in these cases. Though our inquiry is still in progress it seems warranted to record that we have found beryllium in the lungs only in persons with a known beryllium exposure and in persons with an established anthracosis due to coal mining.

The tissues of the coal miners with amounts of beryllium as high as 0.02 γ /G did not contain any lesions comparable to those found in beryllium industry employees. Berylliosis has been diagnosed on histological criteria in the absence of any demonstrable beryllium or when the amount of beryllium present was much less than 0.005 γ /G (our current average for coal miners). The mere presence of beryllium alone, therefore, does not, in the judgment of competent physicians, constitute an adequate factor in the diagnosis of the lesion. This phenomenon is familiar to those of us who have dealt with the problems of silicosis and asbestosis. Thus, in silicosis it is not the total silica which counts, but the proportion of it which is present in the form of free silica. Similarly the presence of asbestos bodies in alveolar spaces or in the sputum alone does not warrant a diagnosis of asbestosis: the asbestos fibrils have to gain entrance to the alveolar walls, where they provoke fibrosis. The asbestos body is probably a mere epiphenomenon and not the causative factor in the disease. The asbestos fibrils which stimulate fibrosis, being usually much smaller than the average asbestos body, are usually invisible by direct microscopy. By analogy we need additional information about the beryllium recovered in a case of suspected berylliosis before we can admit such chemical evidence as a diagnostic criterion. For free silica determination we have x-ray diffraction apparatus and for asbestosis we have electron microscopy to demonstrate the ultimate causative agent. In cases of beryllium disease it has not yet been established in precisely what form the beryllium compound constitutes an etiological agent in the genesis of chronic disease. Probably large numbers of compounds are essentially inert as human pathogens with a few only, and even perhaps only certain crystal patterns among these, having the

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Figure 4.
Diffuse Reticulosis of Alveolar Walls
Lung biopsy from an employee of a beryllium
copper master alloy plant (Hick-hovsky - 175 x)

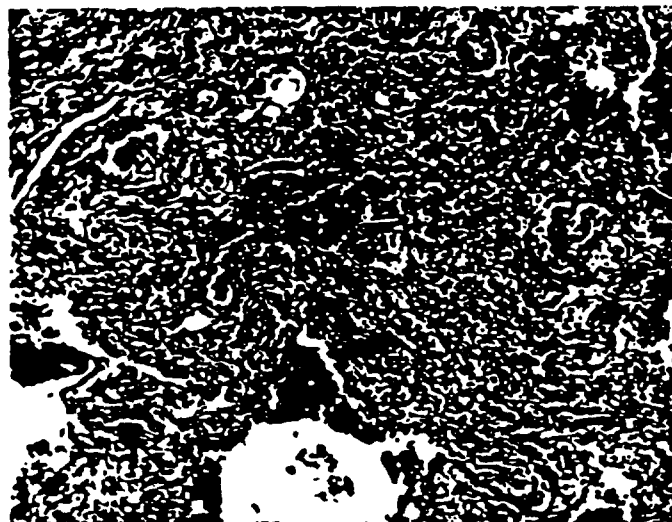


Figure 3.
Diffuse Collagenosis of Alveolar Walls
Exposure to beryllium oxide from a beryllium
copper master alloy plant (Deceased) (Malbury - 175 x)

capacity to cause chronic disease. Many of them are inert with respect to certain animal species.

Such generalizations may fortify the immunity for certain beryllium industries; therefore, that our Saranac Laboratory examples of the chronic disease from one major industry in the country which has produced thousands of pounds. Thus we have cases from industries: the extraction of beryllium from ore and beryllium copper master alloys; cases from beryllium electrical industries; and even a case arising from the fluorescent tube industry has yielded:

Lung Cancer Caused by Beryllium Compounds

One of the more spectacular results from our studies on beryllium concerns the discovery that fluorescent tube powder (zinc beryllium) induced bone sarcoma in rabbits and guinea pigs. It has now been possible to show that beryllium in the compound mixture monary carcinogen has been confirmed by beryllium sulphate (Figure 9). All the lung cancers have already been produced and after a relatively prolonged induction period (and 11).

Though frequently multifocal in origin, malignant, metastasize and would eventually be disturbed. The normal control rats have no similar pulmonary tumors. Not only have we succeeded in retransplanting such tumors to other rats now even to the fifth successive generation. The tumors have retained their capacity to conduct studies on the possible co-carcinogenesis with quartz, iron and asbestos dust. The results of these studies showed that the presence of iron in the lungs of animals exposed

1. Acknowledgement is made to Dr. O. J. Dobrogoski of the Saranac Laboratory for their assistance in the



Figure 4.
Diffuse Reticulosis of Alveolar Walls
Lung biopsy from an employee of a beryl ore
extraction and beryllium copper master alloy
plant (Michalevsky - 175 x)



Figure 3.
Diffuse Collagenosis of Alveolar Walls
Exposure to beryllium oxide from a beryl ore
extraction and beryllium copper master alloy
plant (Deenard, Khilory - 112 x)

capacity to cause chronic disease. Many of these substances certainly are inert with respect to certain animal species (Table 1).

Such generalizations may fortify those who have been claiming immunity for certain beryllium industries. It is necessary to confirm, therefore, that our Saranac Laboratory cases include indisputable examples of the chronic disease from employees of virtually every major industry in the country which has handled beryllium compounds. Thus we have cases from industries primarily concerned with the extraction of beryllium from ore and the manufacturing of beryllium copper master alloys; cases from brass foundries; ceramic and electrical industries; and even a case arising in an atomic pile worker. The fluorescent tube industry has yielded the largest number of cases.

Lung Cancer Caused by Beryllium Compounds

One of the more spectacular results we have recently obtained with our studies on beryllium concerns the production of lung cancer. This discovery was presaged by Doctor Gardner's original demonstration that fluorescent tube powder (zinc beryllium manganese silicate) induced bone sarcoma in rabbits and guinea pigs on intravenous injection. It has now been possible to show that this same substance causes squamous cell carcinomatosis in rats (Figure 8). That it is the beryllium in the compound mixture which constitutes the pulmonary carcinogen has been confirmed with repeated success with beryllium sulphate (Figure 9). All the common varieties of carcinoma have already been produced and the yield of tumors is high after a relatively prolonged induction period (Table 4, Figures 10 and 11).

Though frequently multifocal in origin the tumors are truly malignant, metastasize and would eventually kill the victims if left undisturbed. The normal control rats have never been observed to yield similar pulmonary tumors. Not only have we succeeded in transplanting such tumors to subcutaneous tissues of other rats, but we have succeeded in retransplanting such growth subcutaneously into other rats now even to the fifth successive generation.² Even transplanted tumors have retained their capacity to metastasize. We have conducted studies on the possible co-carcinogenesis of the beryllium with quartz, iron and asbestos dust. The latter study is still in progress but the earlier studies showed that the presence of either quartz or iron in the lungs of animals exposed to the beryllium sulphate

². Acknowledgement is made to Dr. O. J. Dobrogorski and Mr. A. B. Delahant of the Saranac Laboratory for their assistance in the program of tumor transplants.

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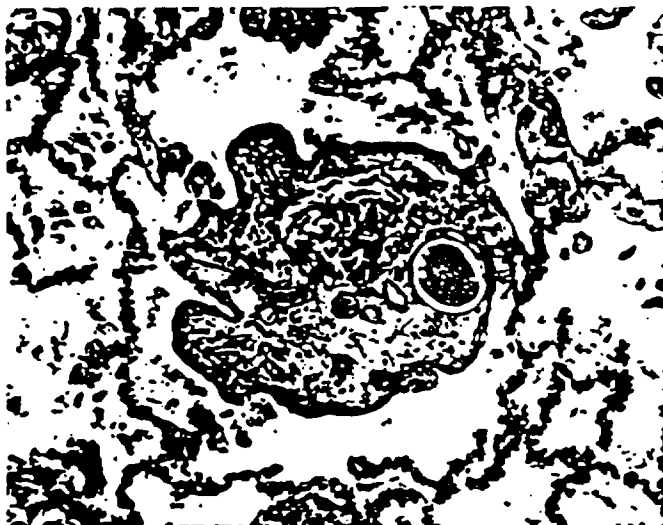


Figure 6.
Pulmonary Granuloma — Rat Lung
Experimentally induced through exposure
to an aerosol of commercial anophthalmos
virus (Muller - 350 x)

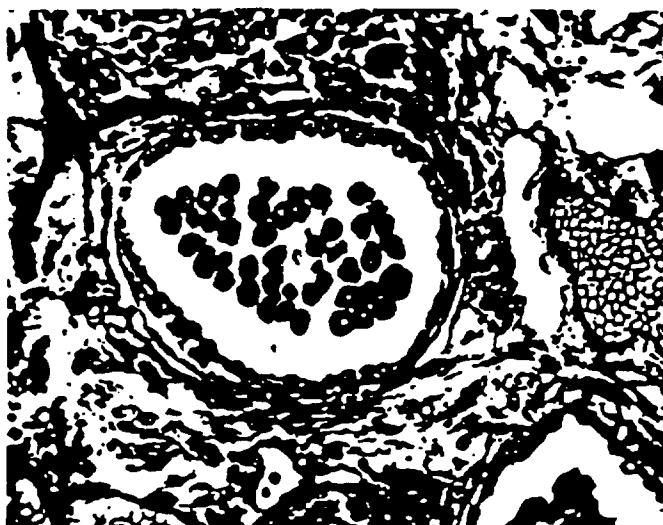


Figure 5.
Epithelialization of Alveolar Walls and
Macrophage Catarrh
Lung biopsy from a person employed in the
disposal of crystalline-containing fluorescent
dye (Muller - 350 x)





Figure 5.
Epithelialization of Alveolar Walls and
Macrophage Catarrh
 Lung biopsy from a person employed in the
 disposal of beryllium-containing fluorescent
 tubes. (Hindry - 320 x)

[152]



Figure 6.
Pulmonary Granuloma — Rat Lung
 Experimentally induced through exposure
 to an aerosol of commercial amorphous
 silica. (Hindry - 320 x)



Figure 7.
Pulmonary Granuloma — Guinea Pig Lung
 Experimentally induced three months after
 intratracheal introduction of beryllium oxide.
 (Von Gienon - 175 x)

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Figure 8.
Squamous Cell Carcinoma — Rat Lung
 Experimentally induced by three months ex-
 posure to zinc beryllium phosphate sulfate
 (Hematoxilin and Eosin - 175 x)

modify the carcinogenic potency of the latter substance perhaps significantly.

These studies pose the grave question whether beryllium may not ultimately prove a factor in the genesis of certain cases of human lung cancer. In this connection the marked proclivity with which the beryllium exposure induces the alveolar lining cells to proliferate may constitute the precursor for a later neoplastic change. All that may be necessary may be an adequate induction period. A recent biopsy specimen from the duorescent tube industry quota of pulmonary disease seems to illustrate the exaggerated degree to which the alveolar epithelium may proliferate. This may constitute a pulmonary variant of carcinoma in situ (Figure 12).

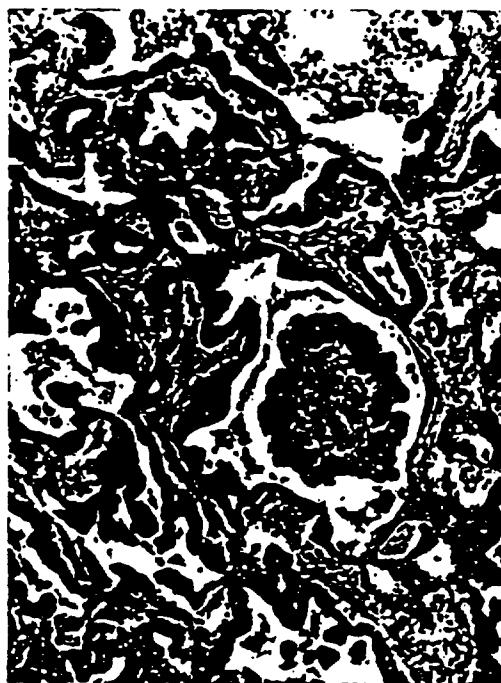


Figure 9.
Pulmonary Adeno-Carcinoma — Rat Lung
Experimentally induced by six months exposure
to beryllium sulphate.
(Hematoxylin and Eosin - 300 x)

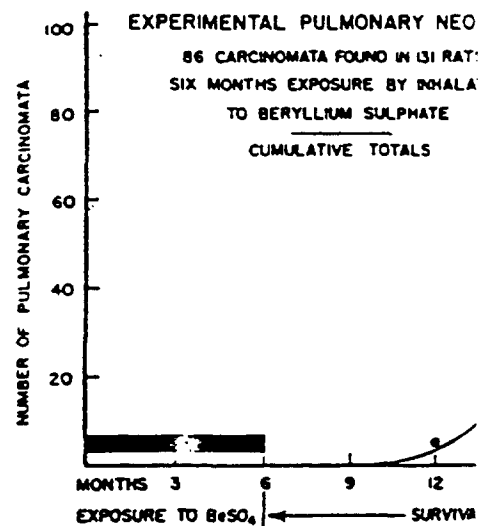


Figure 10.

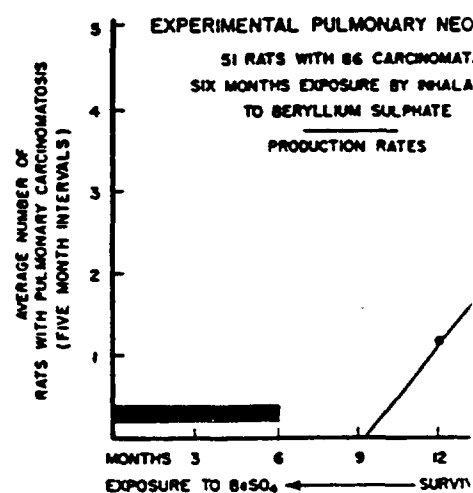


Figure 11.

potency of the latter substance perhaps sig-

the grave question whether beryllium may not be in the genesis of certain cases of human lung cancer, the marked proclivity with which the beryllium alveolar lining cells to proliferate may constitute a later neoplastic change. All that may be a late induction period. A recent biopsy specimen from a tube industry worker shows a pulmonary disease of a degree to which the alveolar epithelium is replaced by a dense cellular mass (Figure 12).



Figure 9.
Adeno-Carcinoma — Rat Lung
Induced by six months exposure
to beryllium sulphate.
(H&E - 300 x)

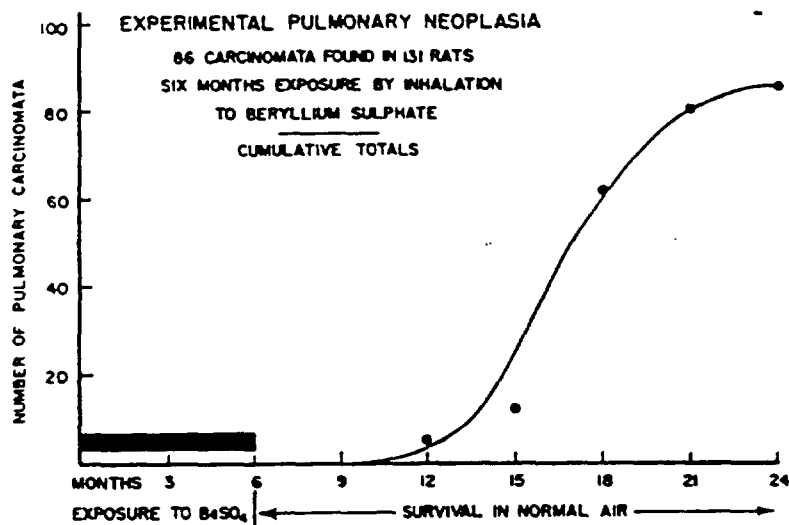


Figure 10.

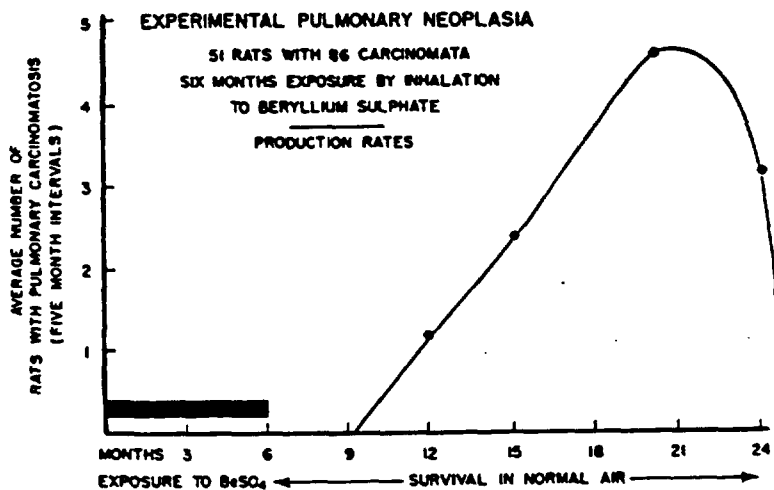


Figure 11.

SUMMARY

1. The whole problem of chronic beryllium disease of the lungs is reviewed in the light of a re-examination of all the human material assembled in the Saranac Laboratory and all the experimental data.

2. It is suggested that the granulomatous form of berylliosis is but one of the many histopathological manifestations of chronic pulmonary beryllium disease.

3. The validity of the beryllium content of suspect lung tissue as a diagnostic criterion is re-examined in view of the fact that coal miners' lungs contain small quantities of the element.

4. Pulmonary cancer has been experimentally produced in rats on exposure to beryllium sulphate and beryllium phosphor and this poses the grave question whether human subjects exposed to beryllium compounds may not eventually develop similar neoplastic pulmonary changes.



Figure 12.
Proliferating Alveolar Epithelium —
Simulating Carcinoma in Situ
Lung biopsy from a person employed in the dis-
posal of beryllium containing fluorescent tubes.
(Stallory - 1700 x)

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