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

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

rly 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- d evaluation of exposure; limits of exposure and power; continuing studies of humans hazard is indicated, the question of methods ivestigated. In the meantime it is strongly to microwaves, particularly from radar protection is particularly important. Some ade of use of special screen glasses for this any problems involved in their use.

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

RECENT OBSERVATIONS ON CHRONIC PULMONARY BERYLLIUM DISEASE

G. W. H. SCHEPERS, M.D., D.Sc.
Director, Saranac Laboratory and Trudeau Foundation

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 Laboratory[1] 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.

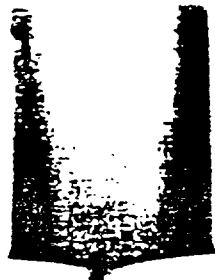

TABLE 1.
Beryllium Compounds Tested for their Capacity to Cause Chronic Lesions and Neoplastic Change.
Saranac Laboratory — 1944-1953

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

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

Rather obviously it is impossible t
data systematically garnered through
be made instead to certain highlights
have topical significance. That new fac
be of interest seems probable, for in n
mystery. Furthermore, although a gre
been applied to the prevention of bery
of new cases have been gratifyingly a
would seem that the danger has by no
increasing importance of beryllium in t
in metallurgy points to the possibility
may yet occur.

Chronic Berylliosis versus Chronic P
Beryllium Workers

This is the first matter which nee
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of pulmonary lesions other than the gra
regarded as the essential component of
question now is whether these non-granu
their own be recognized as pathognomon
ic form of the beryllium disease.

The primary pulmonary manifesta
not present as granulomatous processes.
cheo-bronchitis or a non-specific type of
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berylliosis manifests itself as chronic va
chronic penumonitis. In common practi
nosis of the chronic form of the disease
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ter requiring critical examination. No
nodular chronic lesions. Asbestos and c
By analogy is it not possible that too n
been placed on the granuloma as the
beryllium disease and too little on t
chronic lesions associated with the inhala

A review of the Saranac Laborato
vealed that granulomata constituted the
about two-thirds of the cases (Figure

Beryl	O	O	O											
Beryllium	O		O		O				O	O			—	
Be Carbide			O	—					O	O				
Be Carbonate	O	—		—	—	—	—	—	—	O	—			—
Be Hydroxide	O	—	O		O	—	—	—	O				—	
Be Nitrate	O	—		—	—	—	—	—		O		—		
Be Oxide	O	—	O	O	—	—	G	—	O	O	G	O	O	O
Be Phosphate	O	O							O	O	O	O		
Be Sulphate	O						G				G			
Be Metal plus B.A.L.	O													
Be Glass	O	—				—	—		—	—				
Be Silicate	O	—	—	—	—	—	—	—	—	—				—
Be Stearate	O	—	—	—	—	—	—	—	—		—		—	—
Be Phosphor	N	O	—	O	O	—	O	O	N	N	O	O	O	O
Be Phosphor plus Alumina	—	—	O	—	—	—	—	—	—	—	—	—	—	—

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

Rather obviously it is impossible to present in this paper all the data systematically garnered through these studies. Reference will be made instead to certain highlights of our experiences which may have topical significance. That new facts about beryllium disease may be of interest seems probable, for in many ways this entity is still a mystery. Furthermore, although a great deal of engineering skill has been applied to the prevention of beryllium disease and the numbers of new cases have been gratifyingly and progressively curtailed, it would seem that the danger has by no means been vanquished. The increasing importance of beryllium in the atomic energy industry and in metallurgy points to the possibility that further human exposures may yet occur.

Chronic Berylliosis versus Chronic Pulmonary Disease of Beryllium Workers

This is the first matter which needs clarification. Semantically considered, the issue appears to be tautological. The question to be considered is whether the concept "berylliosis" has not been unduly narrowed down to a limited category of pathological states resulting from exposures to respirable beryllium compounds to the exclusion of pulmonary lesions other than the granulomatous process commonly regarded as the essential component of the pathological entity. The question now is whether these non-granulmatous lesions should also on their own be recognized as pathognomonic manifestations of the chronic form of the beryllium disease.

The primary pulmonary manifestations of beryllium disease do not present as granulomatous processes. There may simply be a tracheo-bronchitis or a non-specific type of chemical pneumonitis. These states have wisely been admitted as acute or subacute forms of berylliosis. It would not seem illogical, therefore, to anticipate that chronic berylliosis manifests itself as chronic varieties of tracheo-bronchitis or chronic penumonitis. In common practice, on the contrary, the diagnosis of the chronic form of the disease has been made dependent on the demonstration of granulomata. This seems illogical and is a matter requiring critical examination. Not all dusts necessarily cause nodular chronic lesions. Asbestos and coal dust are notable examples. By analogy is it not possible that too much emphasis has in the past been placed on the granuloma as the exclusive criterion of chronic beryllium disease and too little on the other non-granulomatous chronic lesions associated with the inhalation of beryllium compounds?

A review of the Saranac Laboratory series of human cases revealed that granulomata constituted the dominant universal lesion in about two-thirds of the cases (Figure 1). In the remaining third,

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		Guinea Pigs
	Rats	Rabbits	Swine	Rats	Monkeys	
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	+	+	+	N & G	Δ	
$BeSO_4$ plus Fe_2O_3	+	+	+	N & G	Δ	
$BeSO_4$ plus Asbestos	+	+	+	Δ	Δ	
$BeSO_4$ plus Fiberglas	+	+	+	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
lium-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 whet
mata should not also be included as ins
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logical phenomena or because of their
the series of cases under review, inter
infiltration (Figure 2) with or withou
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
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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 i
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 puln
possible factors in their genesis, will
this connection reference may be mad
apparent that at least some of the var

Beryllium Oxide	-	+	+	+	—	△	-	+				
Beryllium Phosphate						△						
Beryllium Sulphate						△			N & G	+		
Zn-Be-Mn-Silicate						△			N	△		△
Zn-Be-Mn-Silicate plus A.T.A.						△				△		
Zn-Be-Mn-Silicate plus Cortisone			!			△	+					
Zn-Be-Mn-Silicate plus Mg Tungstate						△	+		N & G	△		
$BeSO_4$ plus Quartz						!	!		N & G	△		
$BeSO_4$ plus Fe_2O_3						!	!			△		
$BeSO_4$ plus Asbestos						!	!		△	△		
$BeSO_4$ plus Fiberglas						!	!		△	△		△

△—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 inconstant finding or entirely absent. In the Laboratory we also have a collection of cases which had been rejected as instances of beryilliosis because no granulomata could be found. Several of these cases had been adequately exposed to beryllium-containing aerosols and their lungs were the seat of abundant chronic lesions of the kind that accompany the granulomata in "acceptable cases." On chemical or spectrographic analysis these lungs yielded as much beryllium as was present in those cases in which a diagnosis of beryllosis was accepted because of the presence of granulomata. The question now arises whether these cases without granulomata should not also be included as instances of chronic beryllium-provoked pulmonary disease, either because of the associated histo-pathological phenomena or because of their high beryllium content. Thus, in the series of cases under review, interstitial or alveolar mural cellular infiltration (Figure 2) with or without collagen fibrosis (Figure 3) or reticulosis (Figure 4) constituted a dominant lesion in about half the cases and was absent in less than eight per cent. Likewise epithelialization of the alveolar walls and prevalence in the alveolar spaces of macrophages of the same kind that occupy the centers of the granulomata occurred with the same frequency (Figure 5). Numerous other histological prevalences could be elicited (Table 3).

Suffice it to record at this stage that while the granuloma is a common feature in chronic beryllium disease, it is not the only significant characteristic of the pathological process and may indeed ultimately prove to be a sign of lesser importance than the accompanying histo-architectonic changes in the lung and, in the absence of the latter, perhaps a sign of inadequate diagnostic value. One is fortified in coming to the latter conservative conclusion because a growing body of experimental evidence affirms that granulomata almost indistinguishable from those long considered pathognomonic for berylliosis may be provoked by submicron amorphous silica dusts as well (Figure 6). The granuloma may thus prove to be a non-specific manifestation of the reaction to inhaled dusts of a wide variety. To make a diagnosis of beryllium disease would in such a case require additional histopathological diagnostic criteria and perhaps the production of proof that at least the specific etiological agent, i.e. the beryllium, is also present.

Evidence concerning the range of dominating histological features which accompany the granulomatous lesions and which collectively constitute the chronic beryllium pulmonary disease process, and the possible factors in their genesis, will be elaborated elsewhere. But in this connection reference may be made to the fact that it is becoming apparent that at least some of the variables in the pathology of beryl-

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.

lium disease may be ascribable to etio beryllium itself or to differences in tl form in which the beryllium is introdu depend also on the dosage, on the speed occurs. on the presence of associated di enigmatic factors concerned in individu probable that the granuloma only arises cal factors are present so that the tr disease may be a non-granulomatous pr

On the experimental side we have that chronic beryllium disease is more Thus we have shown, for instance. tha a primary pulmonary necrosis and diff lium sulphate has a marked propensity of alveolar lining cells with an associa epithelialization of atrophic alveoli. I readily leads to the development of diff these substances may also induce the app ure 7). For long the human chronic dis animal experiments did not yield abunda lomata have since been produced but th appear only after prolonged exposure pounds. The point which has perhaps not altogether overlooked, may be that duplicated rather precisely many of th regularly accompany human beryllium vey of the animal experimentation it wo pounds basically possess the capacity t of macrophages, of plasma cells. and of thelium, to provoke the deposition of col blasts or fibrocytes and to destroy the thelium. Crystal clefts and conchoidal bo phenomena and so may giant cells be structure or its altered biochemical com processes may manifest themselves as as chronic interstitial collagenoses or The actual degree of resemblance betwee in man match rather closely the nuances possible to provoke in animals.

Once it be granted that the granul a sufficient criterion of chronic berylliu additional aforementioned histological f ence of beryllium in the diseased tissues

TABLE 3.
ınt Histological Features in 40 Cases
ulmonary *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

:he table are the numbers of cases showing
ıction.

lium 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

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

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

This question may never be satisfact
of the paucity of cases suitable for stud
induction period for chronic beryllium c
terval between the clinical diagnosis and t
final failure to secure an autopsy. Our c
ing to set minimal effective dosage levels
of record that chronic berylliosis has be
physicians not only in the absence of pro
but even after chemical studies failed t
the reasoning being advanced that the l
viously been present but had since been e
the appropriate biological response. Beryl
on the strength of the demonstration of
ties of the element in the affected tissues.
medical experience that individuals wh
lightly exposed to beryllium compounds c
while other plant personnel apparently m
exposed failed to react. The inverse sens
voked to explain these phenomena. In c
however, the degree of pulmonary react
is a function of dosage and duration of e
able fact that the lungs of human cases
lium disease rather frequently contained
Not all these tissues had previously bee
lium content and perhaps the concept t
exist in the absence of demonstrable q
from an erroneous assumption that failu
beryllium always signified that it had ir
not found. This is not so.

Beryllium is a natural constituent c
(approximately $0.0001\gamma/M^3$)[2] so that th
a lung may not perhaps signify a patholo
lium is present in amounts above a certa
a theoretical possiblity, admittedly remo
Be^7 and Be^{10}, either liberated from ato
cosmic sources, may find their way into
therefore, arises as to what would const
of beryllium in the lung tissue. Reasoni
ers who had spent decades inhaling ear

2. M. Elsenbud - Personal Communication.

6 and less	28		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		61	38.9	16	12.2	5	3.8		

an acceptable medico-legal diagnosis, the new information we have on the latter question becomes critically relevant. How much beryllium is sufficient?

This question may never be satisfactorily settled in man because of the paucity of cases suitable for study, the often relatively long induction period for chronic beryllium disease, the often longer interval between the clinical diagnosis and the autopsy, and the frequent final failure to secure an autopsy. Our current experiments are trying to set minimal effective dosage levels for animals. It is a matter of record that chronic berylliosis has been diagnosed by competent physicians not only in the absence of proof that beryllium is present but even after chemical studies failed to demonstrate its presence, the reasoning being advanced that the beryllium had probably previously been present but had since been excreted, i.e., after provoking the appropriate biological response. Berylliosis has also been diagnosed on the strength of the demonstration of infinitesimally small quantities of the element in the affected tissues. It is a well-known industrial medical experience that individuals who had seemingly been only lightly exposed to beryllium compounds developed the chronic disease while other plant personnel apparently much more heavily and longer exposed failed to react. The inverse sensitization theory has been invoked to explain these phenomena. In our experience with animals, however, the degree of pulmonary reaction to beryllium compounds is a function of dosage and duration of exposure. It is also a remarkable fact that the lungs of human cases of chronic pulmonary beryllium disease rather frequently contained large amounts of beryllium. Not all these tissues had previously been analyzed for their beryllium content and perhaps the concept that the chronic disease may exist in the absence of demonstrable quantities of beryllium arose from an erroneous assumption that failure to report the presence of beryllium always signified that it had in fact been searched for and not found. This is not so.

Beryllium is a natural constituent of the earth's surface burden (approximately $0.0001\gamma/M^2$)[2] so that the discovery of beryllium in a lung may not perhaps signify a pathological process unless the beryllium is present in amounts above a certain critical level. There is also a theoretical possiblity, admittedly remote, however that stratospheric Be^7 and Be^{10}, either liberated from atomic explosions or there from cosmic sources, may find their way into human lungs. The question, therefore, arises as to what would constitute a negligible background of beryllium in the lung tissue. Reasoning that those industrial workers who had spent decades inhaling earth dust would be most likely

[2] M. Eisenbud - Personal Communication.

Figure 2.
Diffuse Cellular Infiltration of Alveolar Walls
Deceased employee of electrical apparatus manufacturing industry. Exposure to beryllium oxide. (Hematoxylin and Eosin - 350 x)

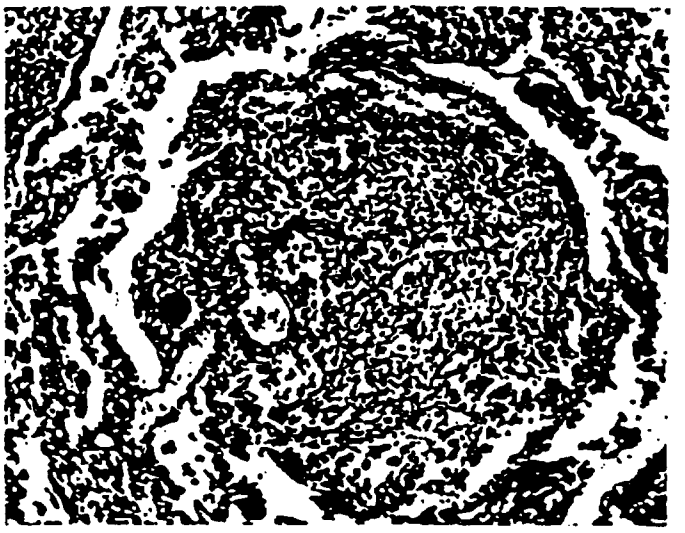

Figure 1.
Pulmonary Granuloma
Deceased employee of a flourescent tube manufacturing plant. Exposure to beryllium phosphor. (Mallory - 175 x)

to show the extreme upper limits of na
tion in the lung, a review of the accumul
the Laboratory was instituted and this s
ditional material from various coal field
contains a relatively high amount of bery
these cases has brought to light that coal
rather regularly contain a small amoun
0.00 to 0.02γ/G dry tissue with an aver
of approximately 0.005γ/G. We have ex
clude a number of non-industrial cases
tuberculosis, but have failed to demonst
lium in these cases. Though our inquiry
warranted to record that we have found
in persons with a known beryllium expo
established anthracosis due to coal minin

The tissues of the coal miners with a
as 0.02γ/G did not contain any lesions c
beryllium industry employees. Berylliosis
tological criteria in the absence of any den
the amount of beryllium present was mu
current average for coal miners). The
alone, therefore, does not, in the judgme
constitute an adequate factor in the di
phenomenon is familiar to those of us wh
lems of silicosis and asbestosis. Thus, in sil
which counts, but the proportion of it w
of free silica. Similarly the presence of
spaces or in the sputum alone does not
bestosis: the asbestos fibrils have to gain e
where they provoke fibrosis. The asbest
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Figure 2.
Diffuse Cellular Infiltration of Alveolar Walls
Deceased employee of electrical apparatus manufacturing industry. Exposure to beryllium oxide. (Hematoxylin and Eosin - 350 x)

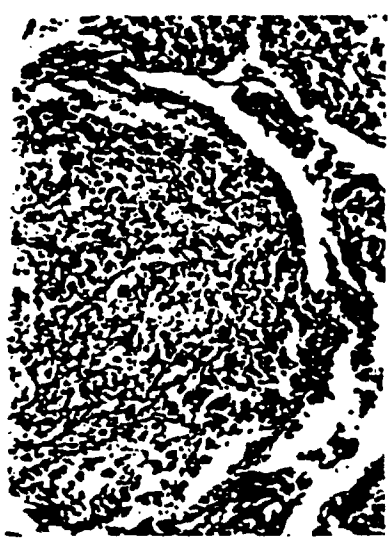

Figure 1.
Pulmonary Granuloma
Deceased employee of a flourescent tube manufacturing plant. Exposure to beryllium phosphor. (Mallory - 176 x)

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 0.02γ/G dry tissue with an average beryllium concentration of approximately 0.005γ/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 0.02γ/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 0.005γ/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

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

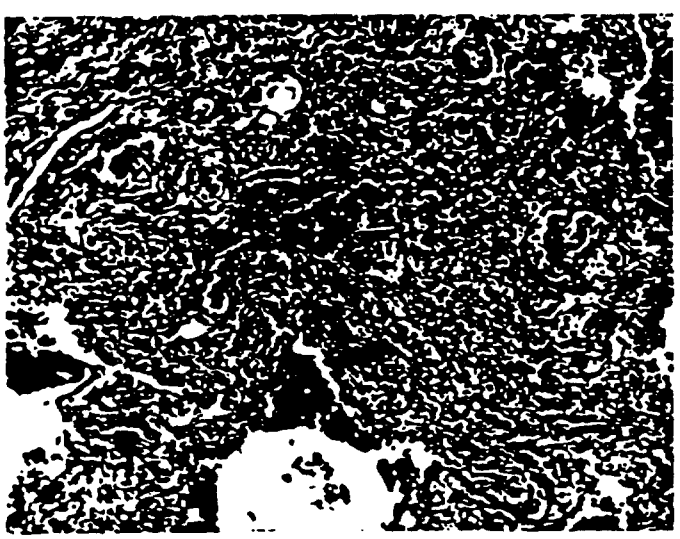

Figure 3.
Diffuse Collagenosis of Alveolar Walls
Exposure to beryllium oxide from a beryl ore extraction and beryllium copper master alloy plant (Saranac Laboratory - 175 x)

capacity to cause chronic disease. Many o
are inert with respect to certain animal sp

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immunity for certain beryllium industries.
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Lung Cancer Caused by Beryllium Com

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1. Acknowledgement is made to Dr. O. J. Dobrogo
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Figure 4.
Diffuse Reticulosis of Alveolar Walls
Lung biopsy from an employee of a beryl ore extraction and beryllium copper master alloy plant (Hitchcock - 175 x)

Figure 3.
Diffuse Collagenosis of Alveolar Walls
Exposure to beryllium oxide from a beryl ore extraction and beryllium copper master alloy plant (Hinkley - 175 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.[3] 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

3. 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 amorphous silica (Ahlbury - 250 x)

Figure 5.
Epithelialization of Alveolar Walls and Macrophage Catarrh
Lung biopsy from a person employed in the shipment of beryllium-containing fluorescent tubes (Ahlbury - 250 x)

[152]

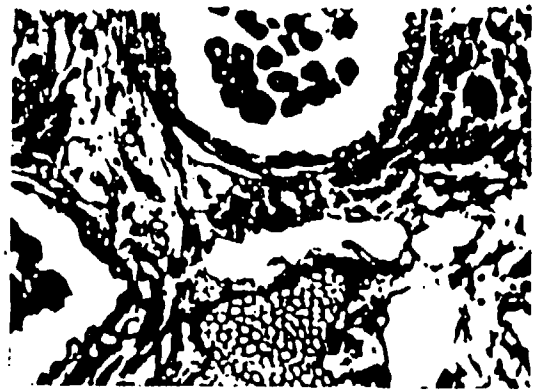

Figure 5.
Epithelialization of Alveolar Walls and Macrophage Catarrh
Lung biopsy from a person employed in the disposal of beryllium-containing fluorescent tubes. (Mallory - 350 x)

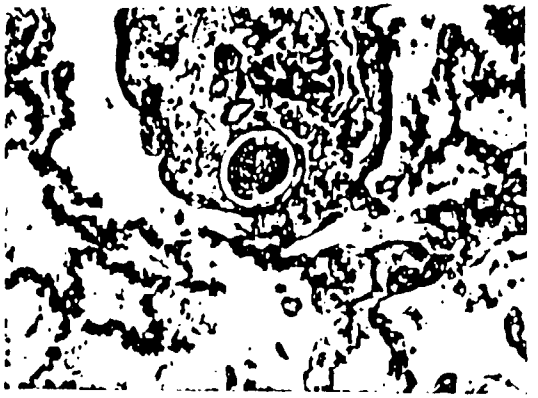

Figure 6.
Pulmonary Granuloma — Rat Lung
Experimentally induced through exposure to an aerosol of commercial amorphous silica. (Mallory - 350 x)

[153]

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

Figure 8.
Squamous Cell Carcinoma — Rat Lung
Experimentally induced by three months exposure to zinc beryllium manganese silicate (Hematoxylin 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 fluorescent 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).

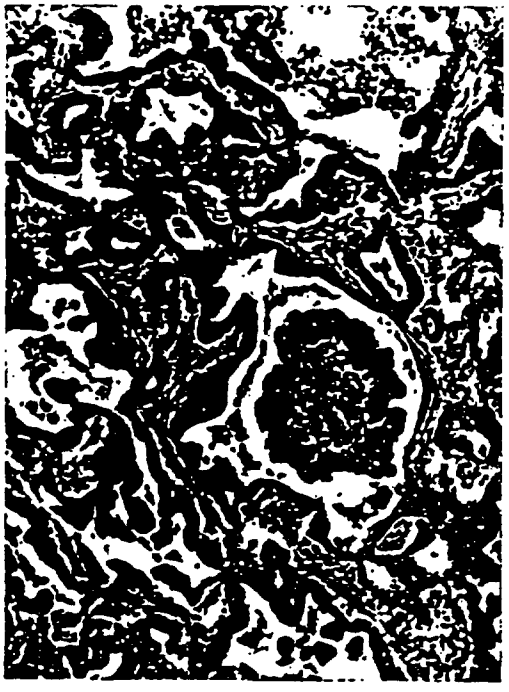

Figure 9.
Pulmonary Adeno-Carcinoma — Rat Lung
Experimentally induced by six months exposure to beryllium sulphate.
(Hematoxilin and Eosin - 300 x)

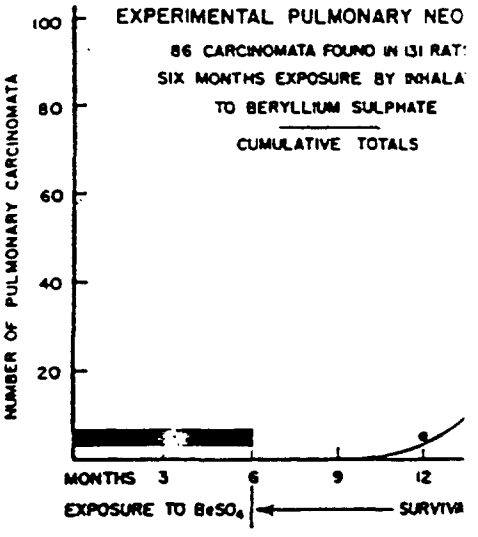

Figure 10.

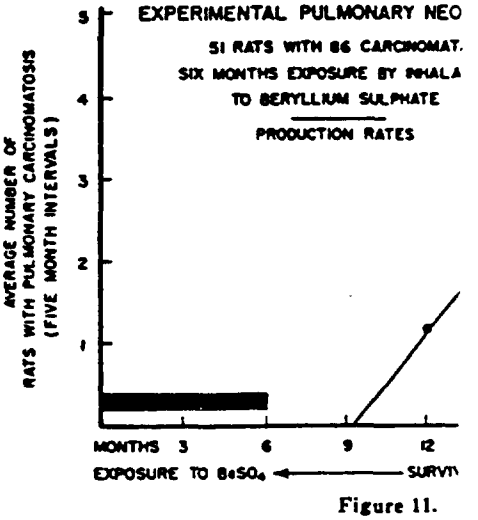

Figure 11.

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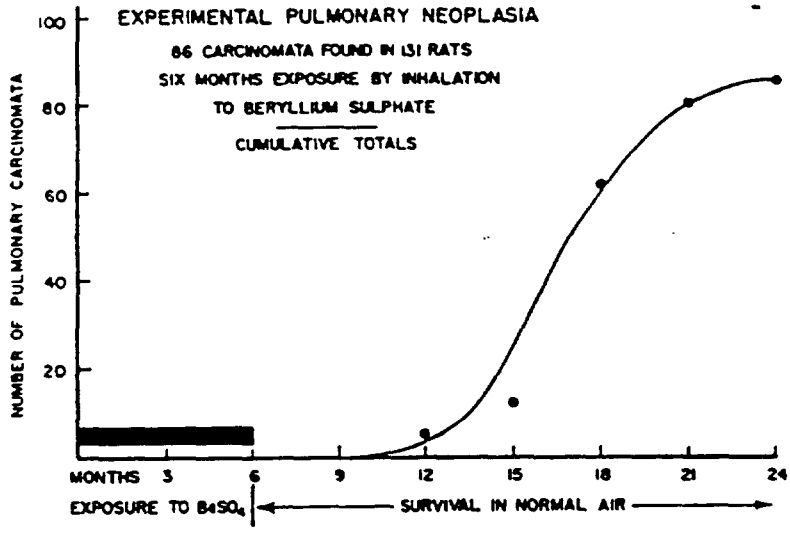

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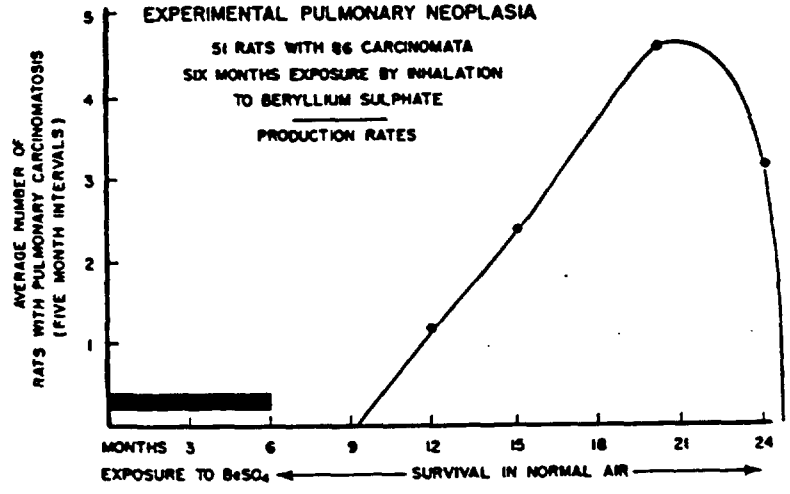

Figure 11.

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 disposal of beryllium containing fluorescent tubes. (Mallory - 1700 x)

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