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Carcinogenicity of Beryllium Hydroxide and Alloys[1]

D. H. GROTH, C. KOMMINENI, AND G. R. MACKAY

Pathology Section, Biological Support Branch, Division of Biomedical and Behavioral Science, National Institute for Occupational Safety and Health, Cincinnati, Ohio 45226

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Animal experiments are presented which show that Be metal, BeAl alloy, passivated Be metal, and beryllium hydroxide are pulmonary carcinogens in rats. These findings are supported by successful transplantation experiments. In addition, other alloys of Be, VBe_{12}, $TiBe_{12}$, $TaBe_{12}$, $NbBe_{12}$, Be_2B, and Be_4B were found to produce pulmonary metaplasia, frequently a preneoplastic lesion in rats. Old rats are shown to be more susceptible to the induction of pulmonary metaplasia than young adult rats. These results indicate that a lower dose of Be would be required to produce cancer in old animals compared to young adult animals. A discussion on the lung cancer incidence in beryllium production workers is presented.

INTRODUCTION

The carcinogenic effects of beryllium compounds in animals have been known since 1946 (Gardner and Heslington, 1946). At least 17 different senior authors have published 27 articles that demonstrated the carcinogenicity in laboratory animals of beryllium compounds (Groth, 1980). The purposes of this series of experiments reported in this article were: to compare the abilities of various beryllium alloys and intermetallics to induce metaplasia or cancer, to determine the carcinogenic effects of beryllium hydroxide ($Be(OH)_2$), and to determine the effect of age on the induction of metaplasia by $Be(OH)_2$. These experiments were performed between 1967 and 1977 and are reported here in the scientific literature for the first time.

CARCINOGENICITY OF BE ALLOYS

The following experiment was conducted to determine the relative carcinogenicities of Be metal (100% Be), passivated Be metal (99% Be, 0.26% Cr), BeAl alloy (62% Be, 38% Al), BeCu alloy (4% Be, 96% Cu), BeCuCo alloy (2.4% Be, 0.4% Co, 96% Cu), and BeNi alloy (2.2% Be, 97.8%Ni). The metals were ground to respirable particle sizes. Geometric mean particle sizes for various samples as determined by electron microscopy varied from 1 to 2 μm. Twelve groups of 3-month-old female, Wistar-derived rats (35 rats/group) were used. All rats in each group received a single intratracheal injection with either 2.5 or 0.5 mg of one of the above metals suspended in 0.4 cc of isotonic saline followed by 0.2 cc of saline. Forty controls were injected with 0.6 cc of saline. The animals were housed (four/cage) in galvanized wire-mesh cages and given commercial rat chow and tap water *ad lib*. They were sacrificed and autopsied at various intervals from 1 to 18 months postinjection. Because of high mortality and cannibalism, there

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were fewer rats available for autopsy (3–21 rats/group) 16–19 months postinjection than originally planned. The greatest number of losses occurred in the groups in which lung neoplasms were found.

Pale yellow nodules varying from 1 to 10 mm in diameter were detected at autopsy in the lungs of rats injected with Be metal, passivated Be metal, and BeAl alloy. Cut surfaces of these nodules were solid and pale yellow or gray. Since these were suspect neoplasms and possibly malignant, pieces of one or two nodules from each of nine rats were transplanted subcutaneously to the axillae of weanling female rats of the same strain and from the same supplier. Tissue remaining after the transplant was prepared for histologic examination. The lungs were inflated with formalin and mediastinal lymph nodes and pieces of liver, spleen, kidney, pancreas, and adrenals from each rat were fixed in formalin. Sections of each lobe of the lungs and the other sampled tissues were stained with hematoxylin and eosin and examined by light microscopy.

The only pathologic changes related to the treatments were confined to the lungs and lymph nodes. Lung neoplasms were observed in animals injected with both the high and low doses of Be metal, passivated Be metal, and BeAl alloy. No lung neoplasms were observed in rats injected with the other compounds. Most of the neoplasms were adenocarcinomas and adenomas; however, two epidermoid carcinomas and at least one poorly differentiated carcinoma were seen in more than 32 lung neoplasms examined. Bronchiolar alveolar cell tumors were present in abundance in the rats injected with Be metal, passivated Be metal, and BeAl alloy. However, because of the lack of generally accepted pathologic criteria for distinguishing between alveolar cuboidal and columnar cell metaplasia and bronchiolar alveolar cell tumors, the incidence of these tumors is not included. The histologic criteria used in diagnosing these lesions were described previously by the senior author (Wagner *et al.*, 1969). All stages of cuboidal, columnar, and squamous cell metaplasia could be seen on the alveolar walls in the lungs of rats injected with the compounds that produced neoplasms. These lesions were identical to those that have been described before (Schepers *et al.*, 1957, 1961; Vorwald *et al.*, 1959). They were generally reduced in size and number or absent from the lungs of animals injected with the other compounds (BeCu, BeCuCo, BeNi). Metastases to a mediastinal lymph node from a primary pulmonary epidermoid carcinoma induced by Be metal were seen in one animal. The lung neoplasm incidences at each autopsy interval and the statistical significance of these incidences at the 16- to 19-month interval are presented in Table 1. The Fisher's Exact Test (Hays, 1963), a one-tailed test, was used. Because of multiple (six) comparisons with the control group, each individual comparison with the control group must have a P value ≤ 0.008 for the overall α-level to be equal to 0.05 (Neter and Wasserman, 1974) and for the results to be statistically significant. The incidences of lung neoplasms in the groups that received 2.5 mg of Be metal, and 2.5 and 0.5 mg of passivated Be metal, were significantly different from controls. Although the incidence (2/6) of lung neoplasms in the group injected with 2.5 mg of BeAl alloy was not statistically significant when compared with the incidence (0/21) in the controls ($P = 0.043$), it was significant ($P = 0.004$) when compared to the incidence (0/84) in the animals that were injected with BeCu, BeNi, and BeCuCo

TABLE 1
BERYLLIUM ALLOYS—LUNG NEOPLASMS

Compounds	Dose of compound (mg)	Dose of Be (mg)	Total No. rats autopsied	Autopsy intervals and lung neoplasm incidences (months) 1	2–7	8–10	11–13	16–19	P value[a]
Be metal	2.5	2.5	16	0/5[b]	—	—	3/5	6/6	<0.0001
Be metal	0.5	0.5	21	0/5	0/3	0/5	0/5	2/3	0.011
Passivated Be metal	2.5	2.5	26	0/5	0/2	1/5	4/10	4/4	<0.0001
Passivated Be metal	0.5	0.5	20	0/5	0/1	0/3	—	7/11	0.0001
BeAl alloy	2.5	1.55	24	0/5	0/3	2/5	0/5	2/6	0.043
BeAl alloy	0.5	0.3	21	0/5	—	0/1	0/6	1/9	0.30
4% BeCu alloy	2.5	0.1	28	0/5	0/1	0/5	0/6	0/11	
4% BeCu alloy	0.5	0.02	24	0/5	0/2	—	0/4	0/13	
2.2% BeNi alloy	2.5	0.056	28	0/5	0/1	0/5	0/5	0/12	
2.2% BeNi alloy	0.5	0.011	27	0/5	0/2	—	0/5	0/15	
2.4% BeCuCo alloy	2.5	0.06	33	0/5	0/3	0/5	0/5	0/15	
2.4% BeCuCo alloy	0.5	0.012	30	0/5	0/2	—	0/5	0/18	
Saline	—	—	39	0/5	0/3	0/5	0/5	0/21	

[a] *P* value (Fisher's one-tailed test) when the lung neoplasm incidence in exposed groups is compared with the lung neoplasm incidence in the saline control group at the autopsy period of 16–19 months. Because of multiple comparisons with the control group, the individual *P* value must be 0.008 or less to be significant.

[b] Number of rats with a lung neoplasm divided by total number of rats autopsied at the specified interval.

alloys containing much lower concentrations of Be and autopsied at the 16- to 19-month interval. In addition, no lung neoplasms have been detected in any control Wistar-derived rats (more than 200 rats) that have been autopsied at 19–21 months of age or older in several experiments from 1964 to 1978 in this laboratory.

The transplantation experiments were successful. Seven of the nine suspect tumors grew upon transplantation, and were first palpated 12–54 weeks post-transplantation. One primary epidermoid carcinoma (Fig. 1) induced by Be metal grew to a size of 3.5 cm within 17 weeks (Fig. 2) and metastasized to the host's lungs. Three of four primary pulmonary adenocarcinomas (Figs. 3 and 4), one of one poorly differentiated carcinoma (Figs. 7 and 8), and one neoplasm whose original cell type was not determined grew upon transplantation (Figs. 5, 6, 9, and 10). All transplanted tumor types metastasized to the lungs of their hosts. Figures 11, 12, and 13 illustrate the pulmonary metastases from a transplanted poorly differentiated carcinoma.

From one to three lung tumors induced by each of the three compounds (Be metal, passivated Be metal, and BeAl Alloy) were thus successfully transplanted. The one bronchiolar alveolar cell tumor that was transplanted did not grow.

CARCINOGENICITY OF BERYLLIUM HYDROXIDE

The following experiment was part of a larger study designed to determine the influence of various factors on the carcinogenicity of beryllium. Two groups of female, Wistar-derived rats, 35 rats per group, were used in this study. The animals were obtained when they were 45–55 g in weight and housed in stainless-

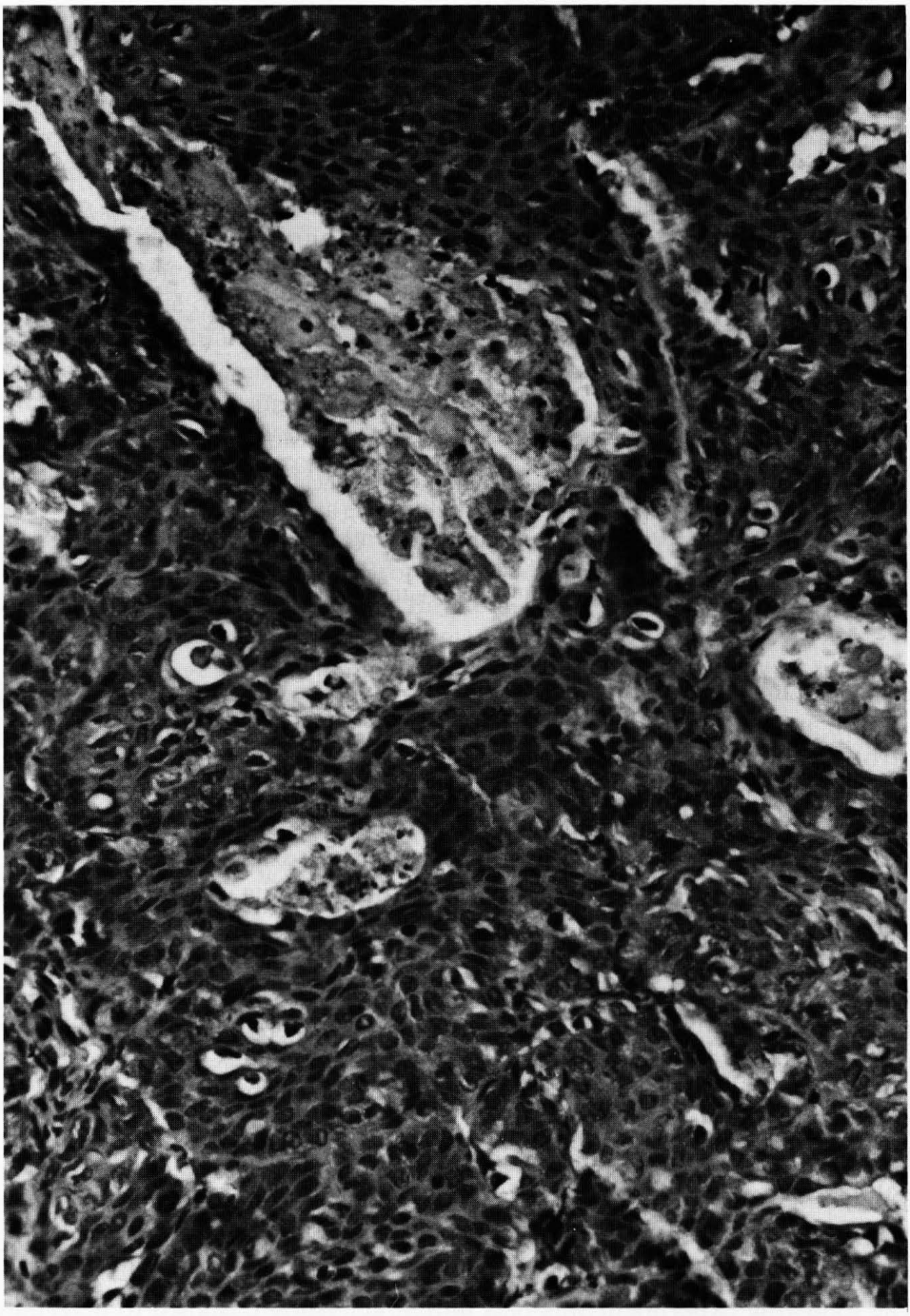

FIG. 1. Primary epidermoid carcinoma of the lung (68-478) induced with 2.5 mg of Be metal. 380×.

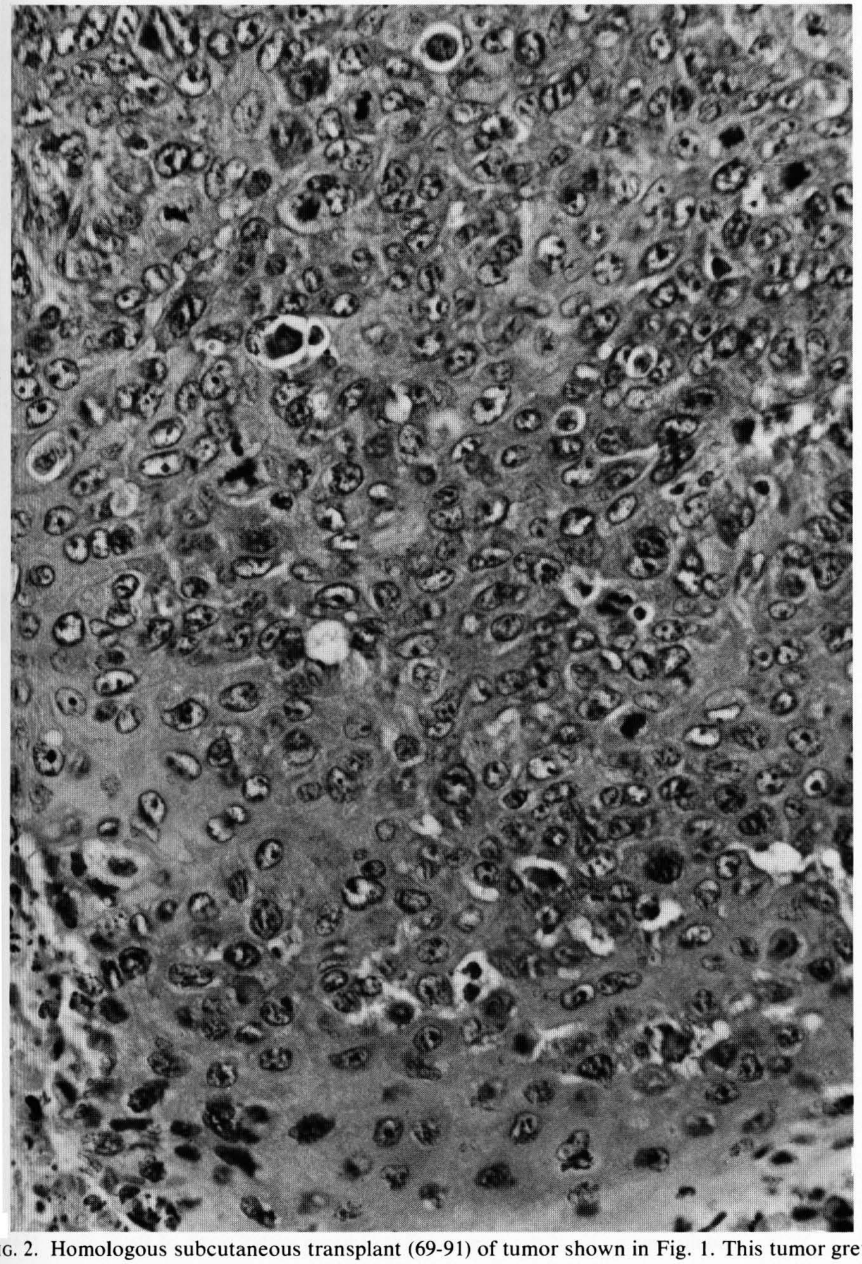

FIG. 2. Homologous subcutaneous transplant (69-91) of tumor shown in Fig. 1. This tumor grew to 3.5 cm in diameter in 17 weeks and metastasized to the lungs. 380×.

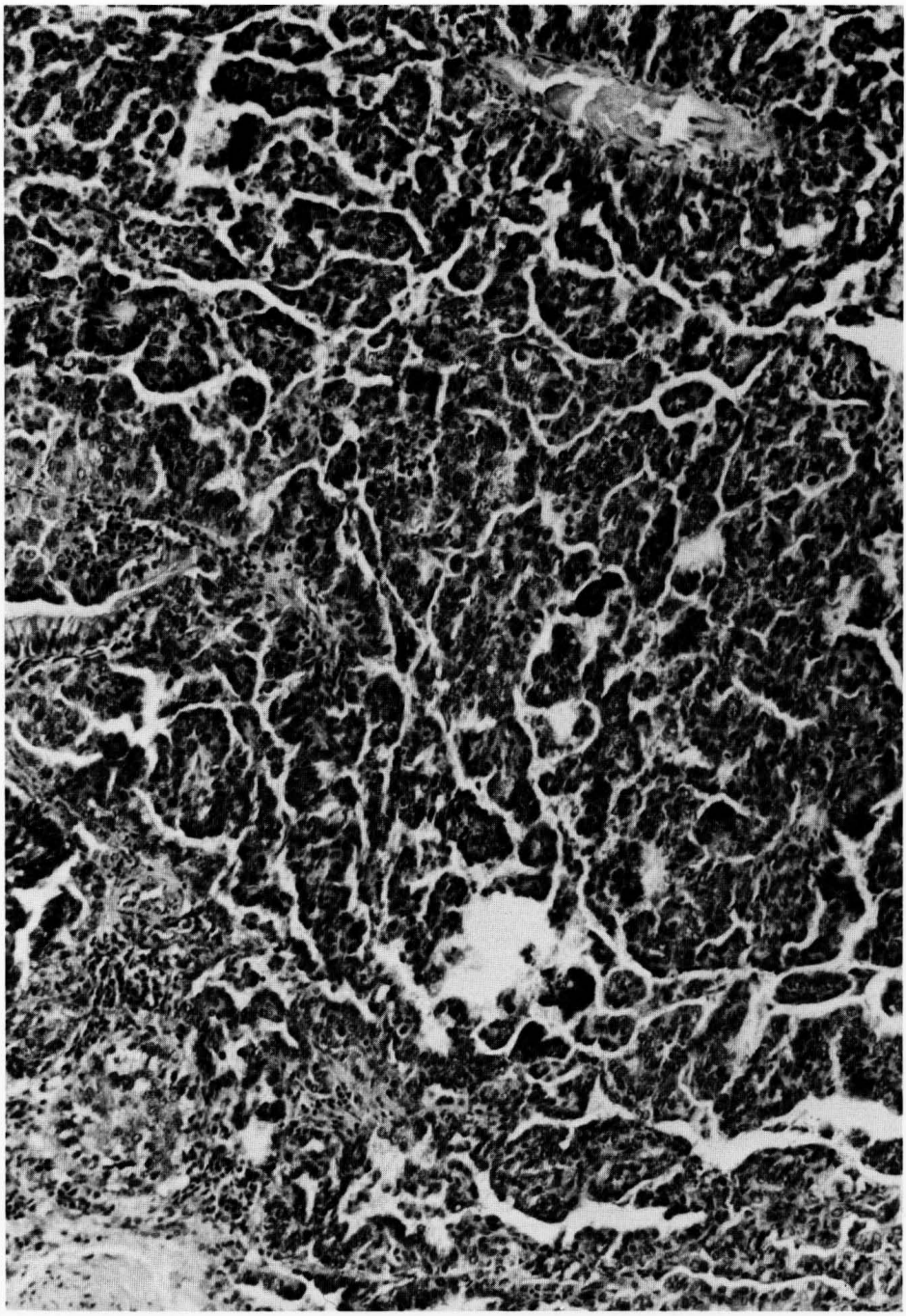

FIG. 3. Primary adenocarcinoma of the lung (68-538) induced with 2.5 mg of BeAl alloy. 154×.

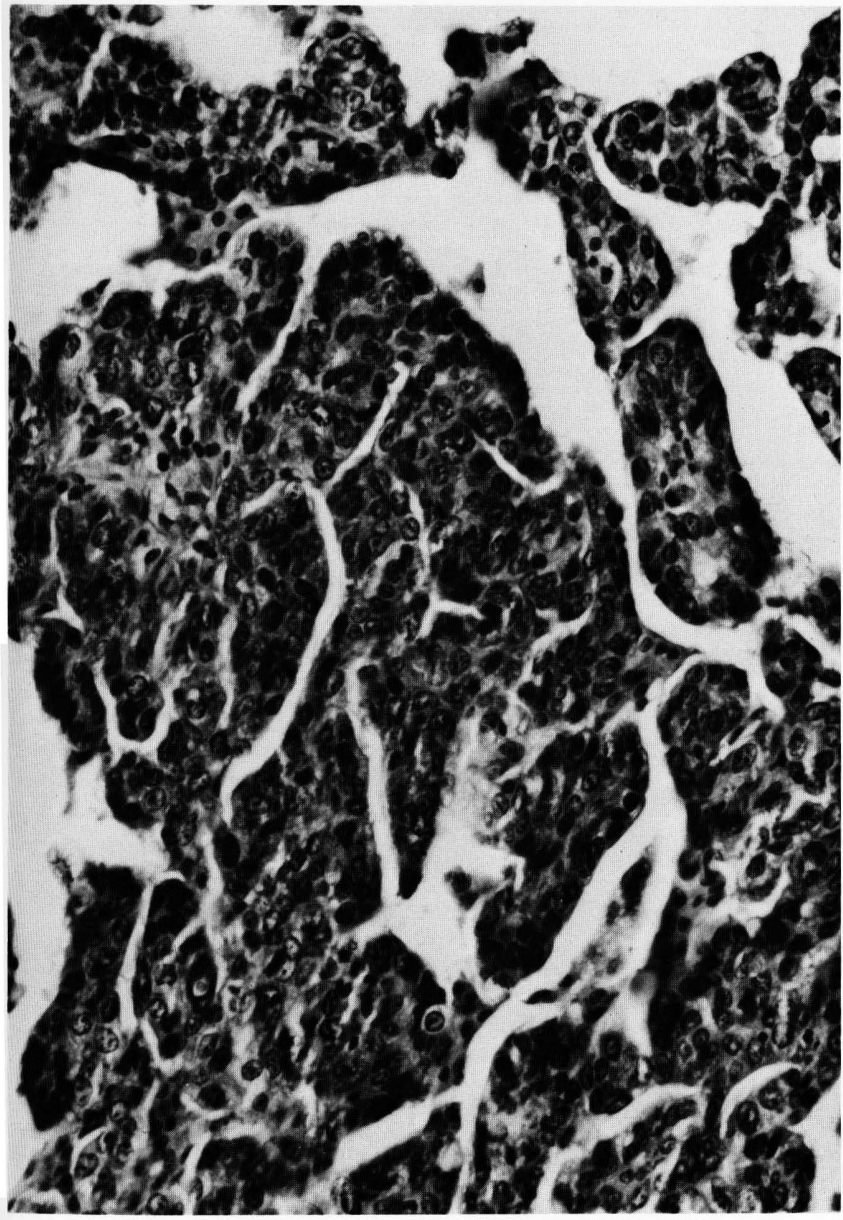

FIG. 4. Same tumor as in Fig. 3, but higher magnification. 380×.

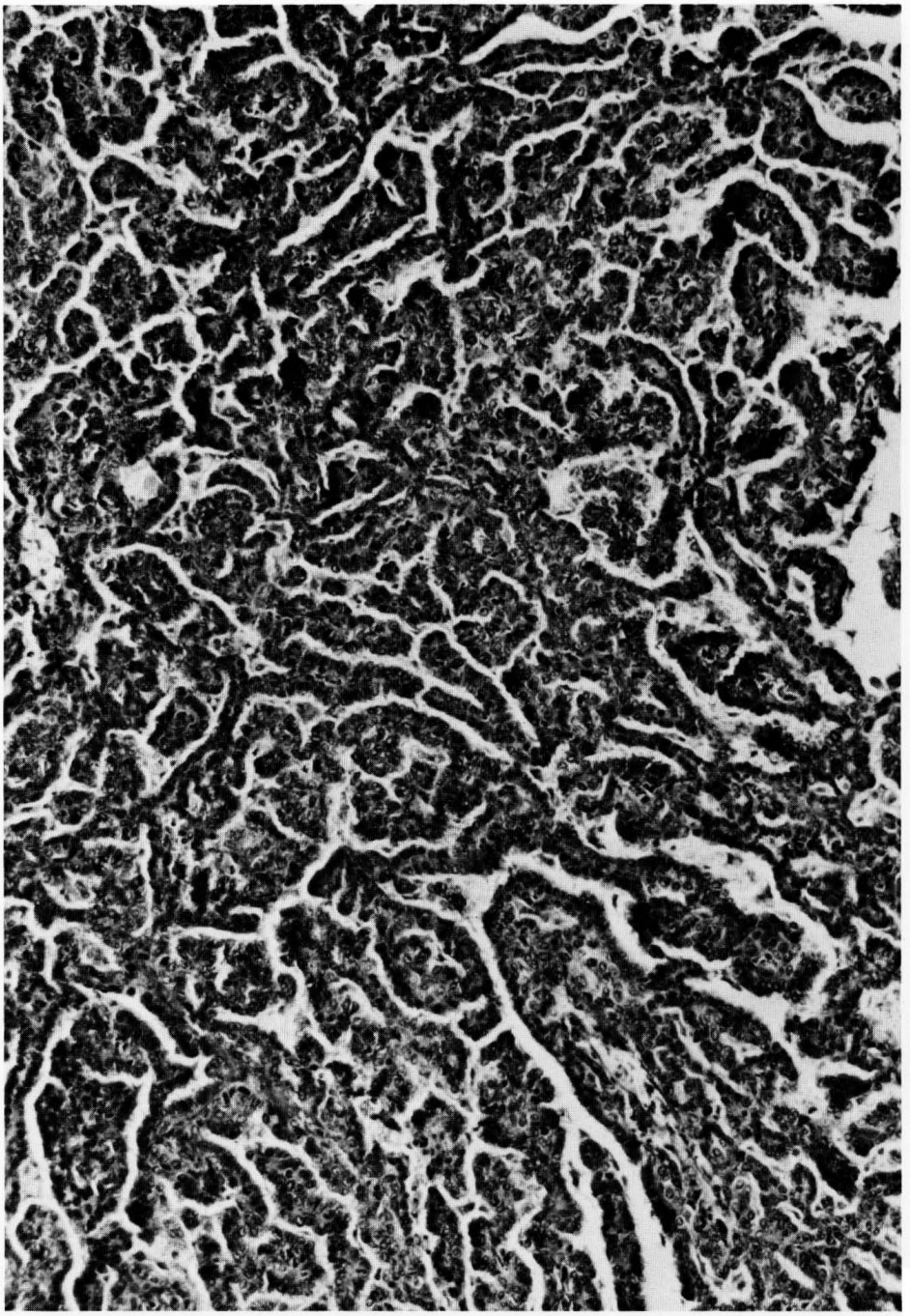

FIG. 5. Homologous subcutaneous transplant (69-872) of tumor shown in Fig. 3 and 4. This transplant grew to 8 cm in diameter in 54 weeks and metastasized to the host's lungs. 154×.

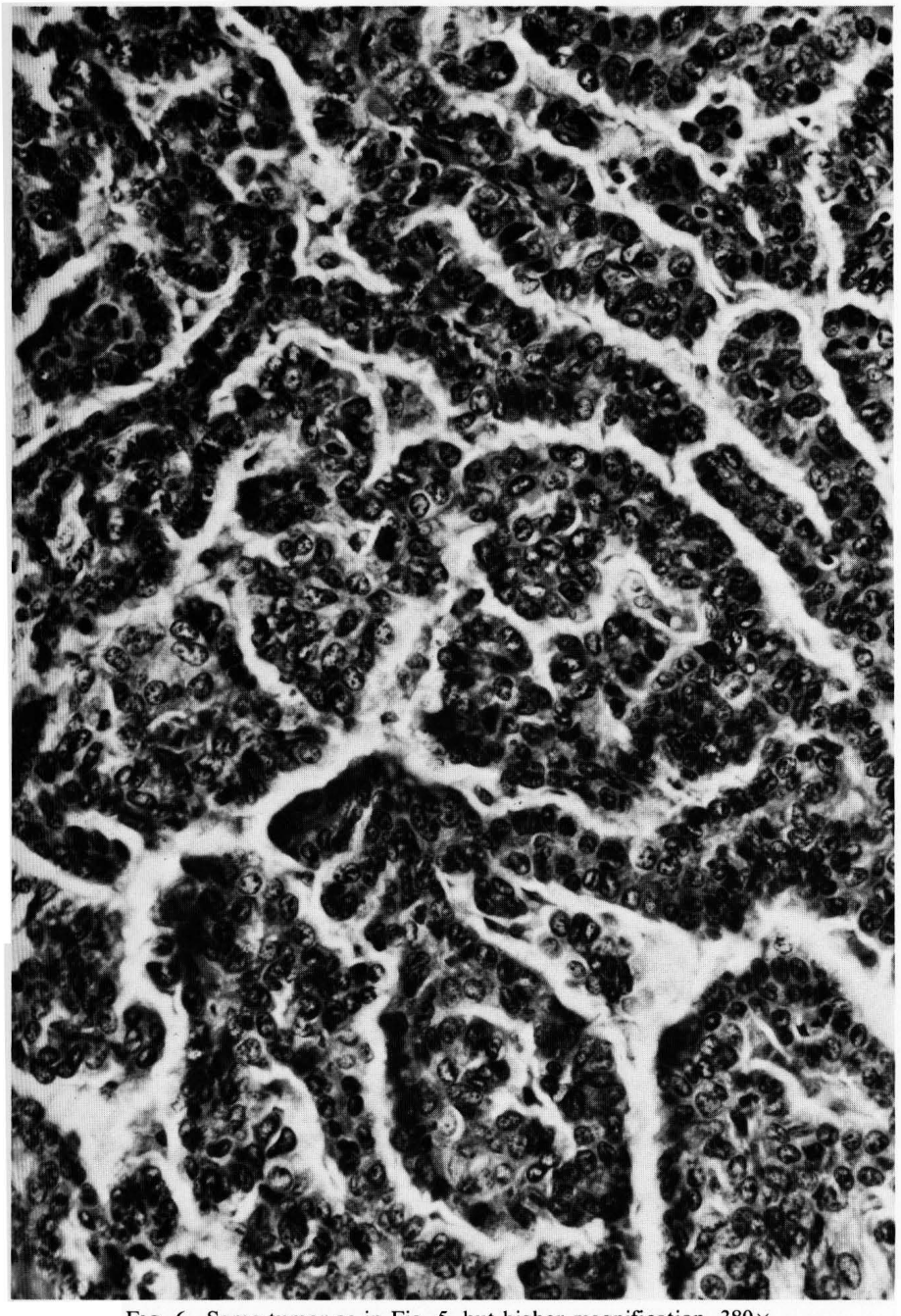

FIG. 6. Same tumor as in Fig. 5, but higher magnification. 380×.

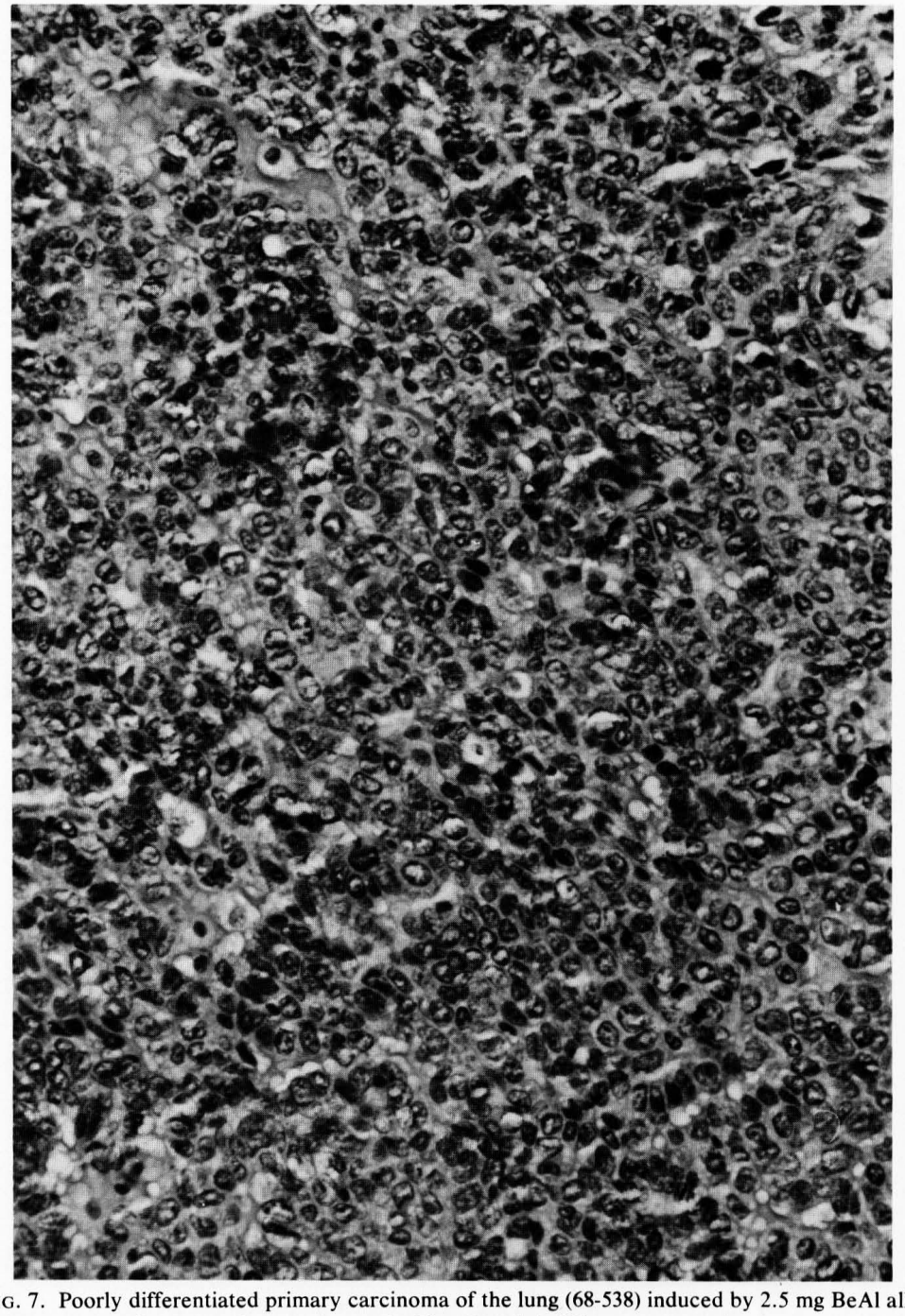

FIG. 7. Poorly differentiated primary carcinoma of the lung (68-538) induced by 2.5 mg BeAl allo
This tumor was adjacent to the tumor seen in Figs. 3 and 4. 380×.

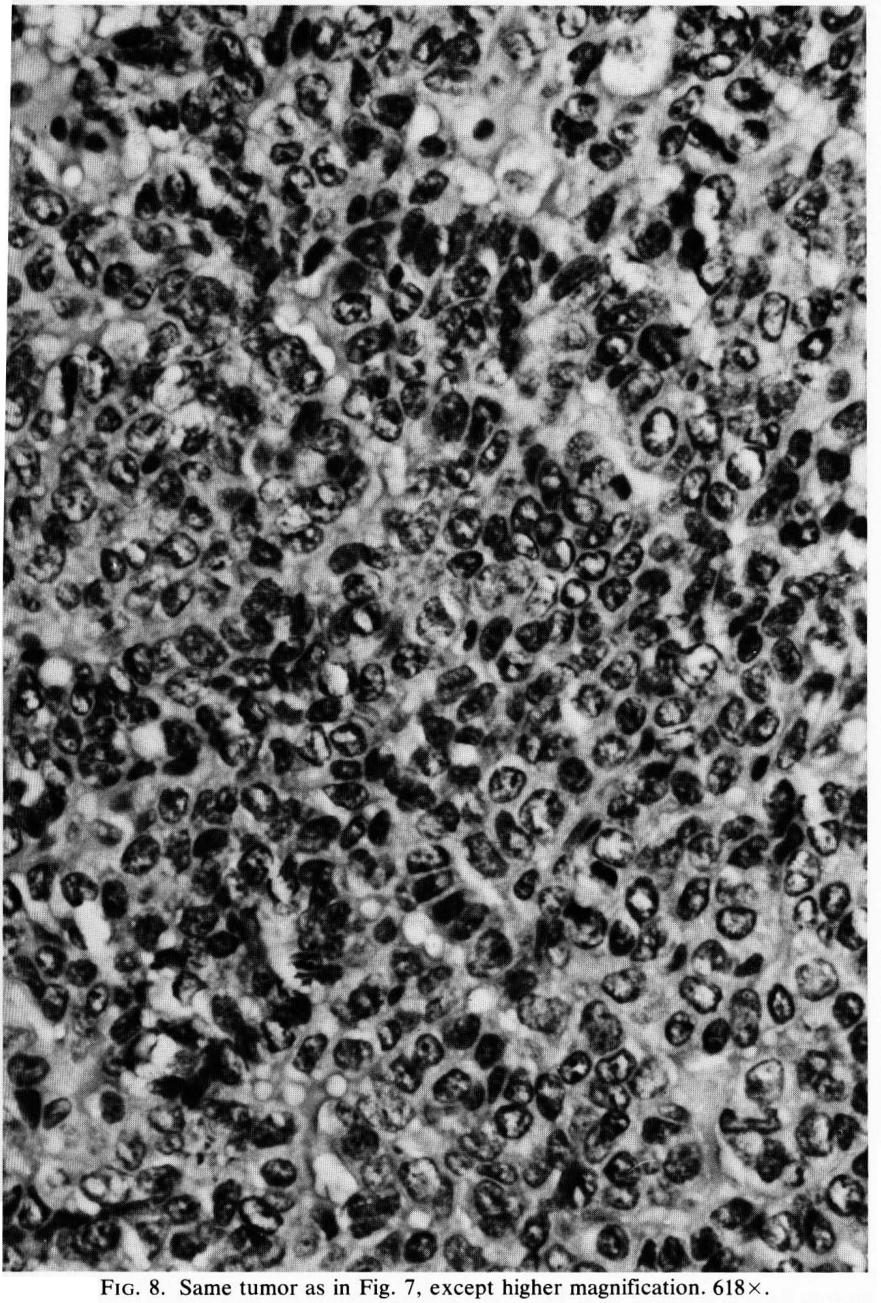

FIG. 8. Same tumor as in Fig. 7, except higher magnification. 618×.

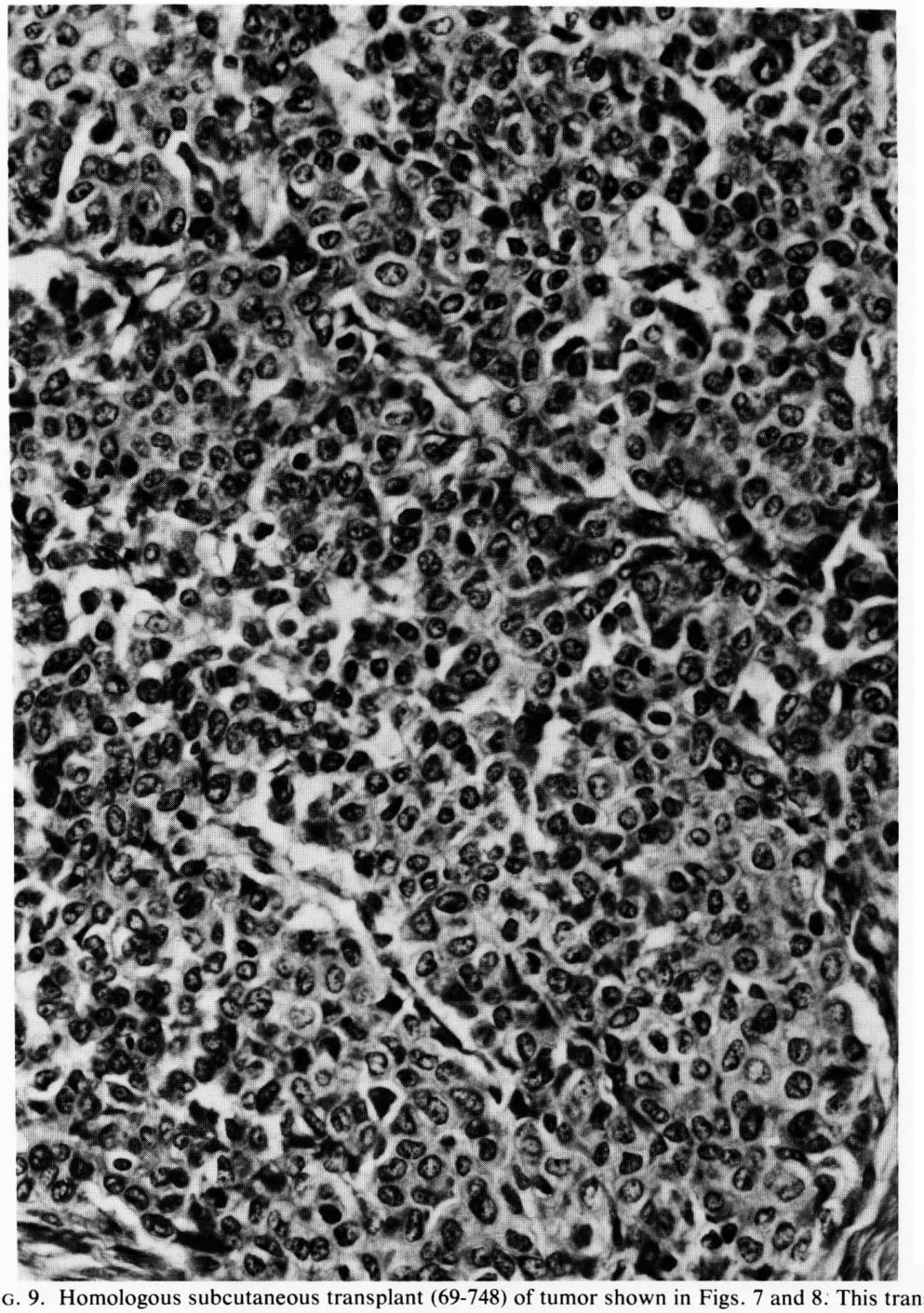

FIG. 9. Homologous subcutaneous transplant (69-748) of tumor shown in Figs. 7 and 8. This transplant grew to 8 cm in diameter in 57 weeks and metastasized to the host's lungs. 380×.

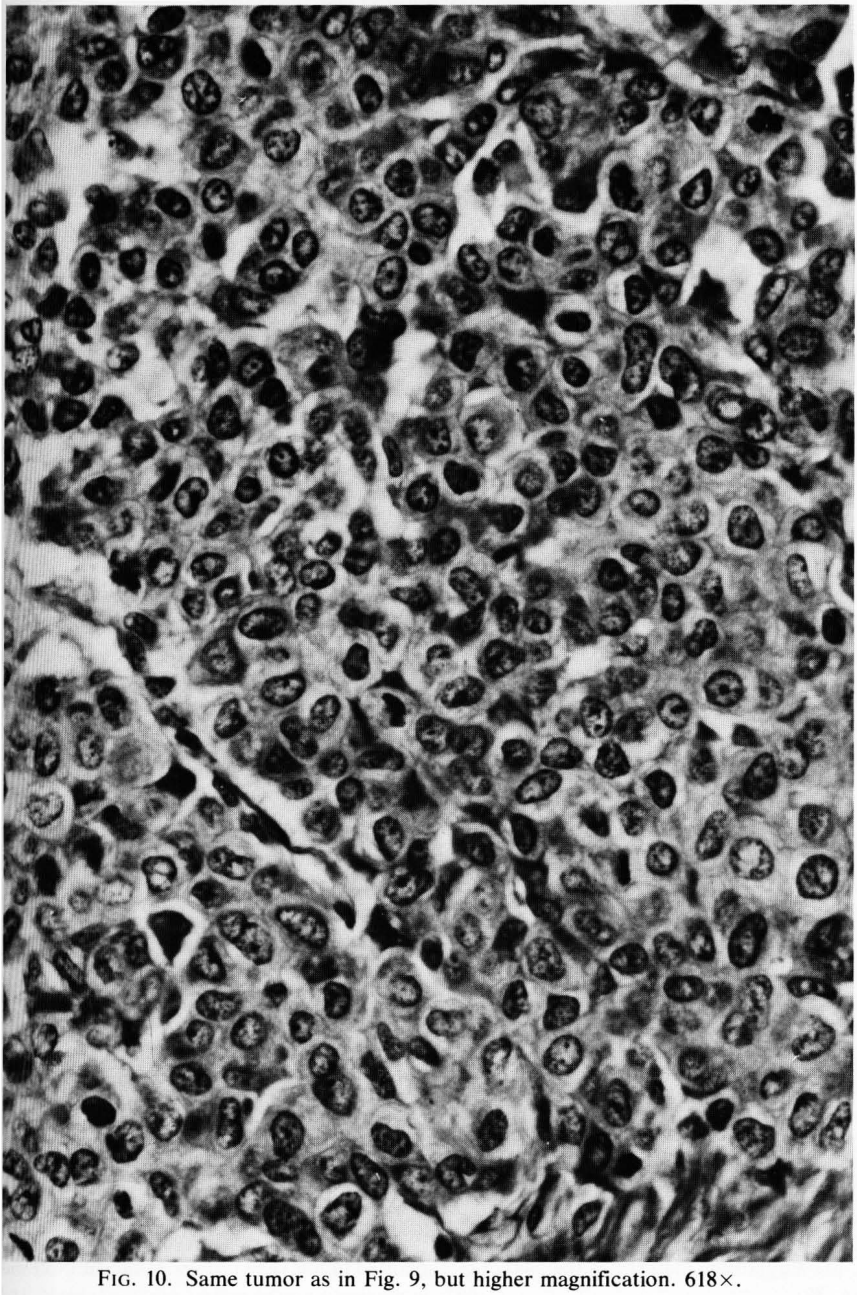

FIG. 10. Same tumor as in Fig. 9, but higher magnification. 618×.

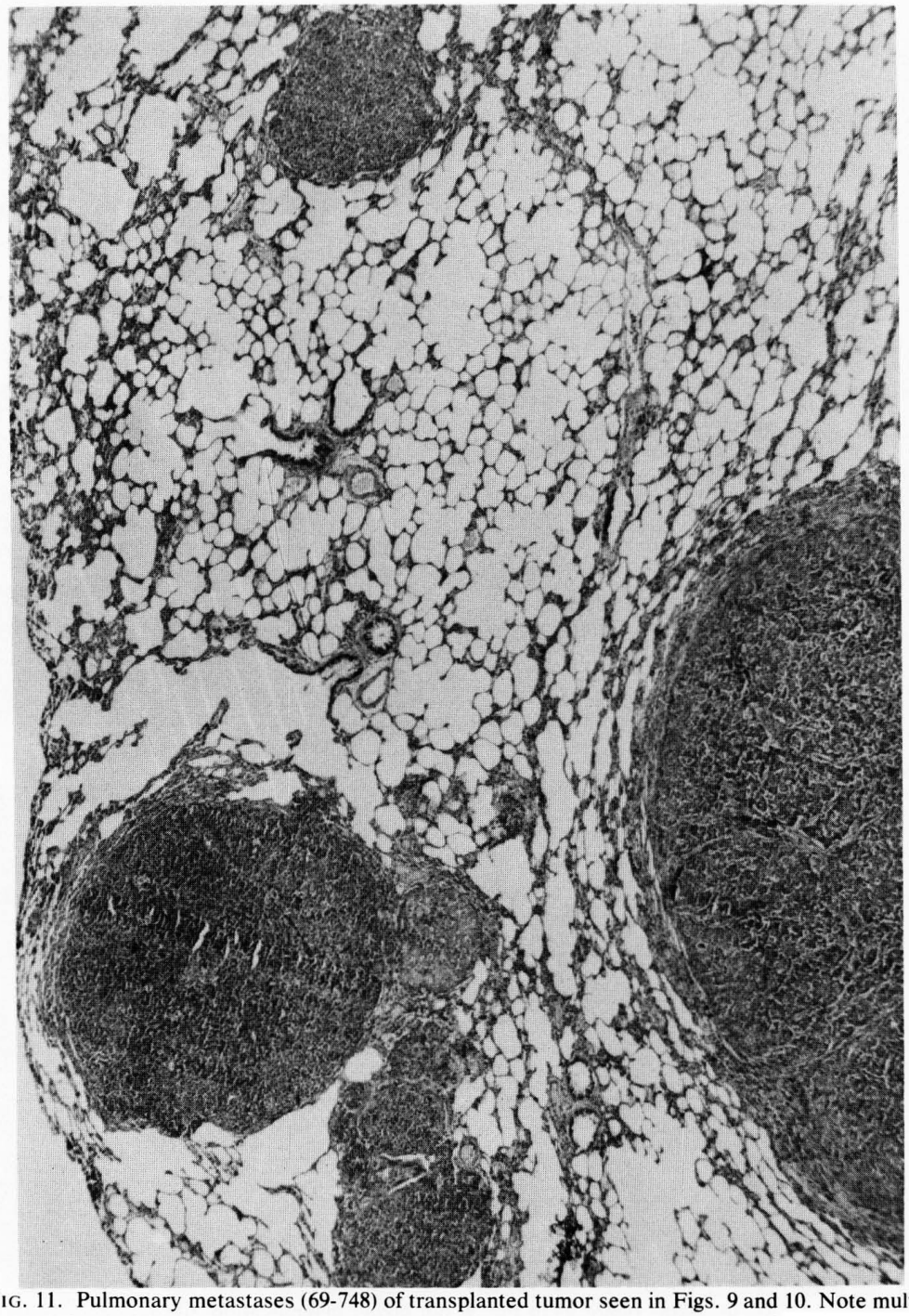

FIG. 11. Pulmonary metastases (69-748) of transplanted tumor seen in Figs. 9 and 10. Note multiple nodules. 38×.

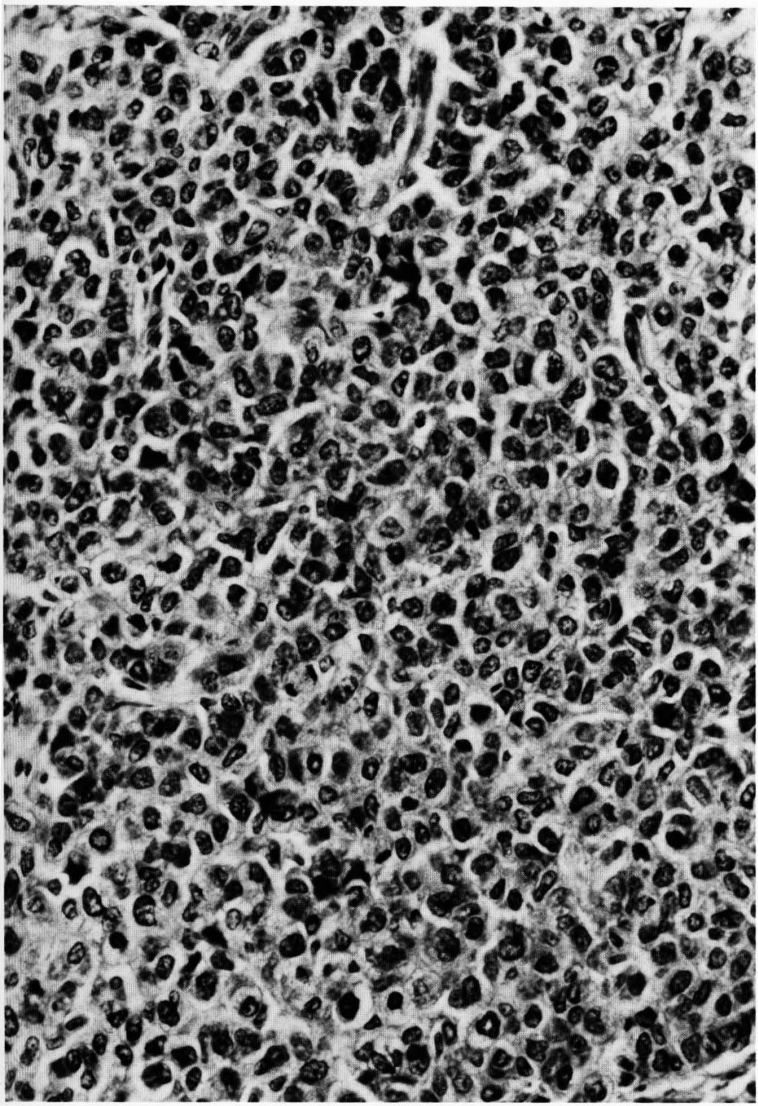

FIG. 12. Pulmonary metastasis (69-748) of transplanted undifferentiated carcinoma seen in Figs. 10 and 11. Note similarity to the primary transplant. 380×.

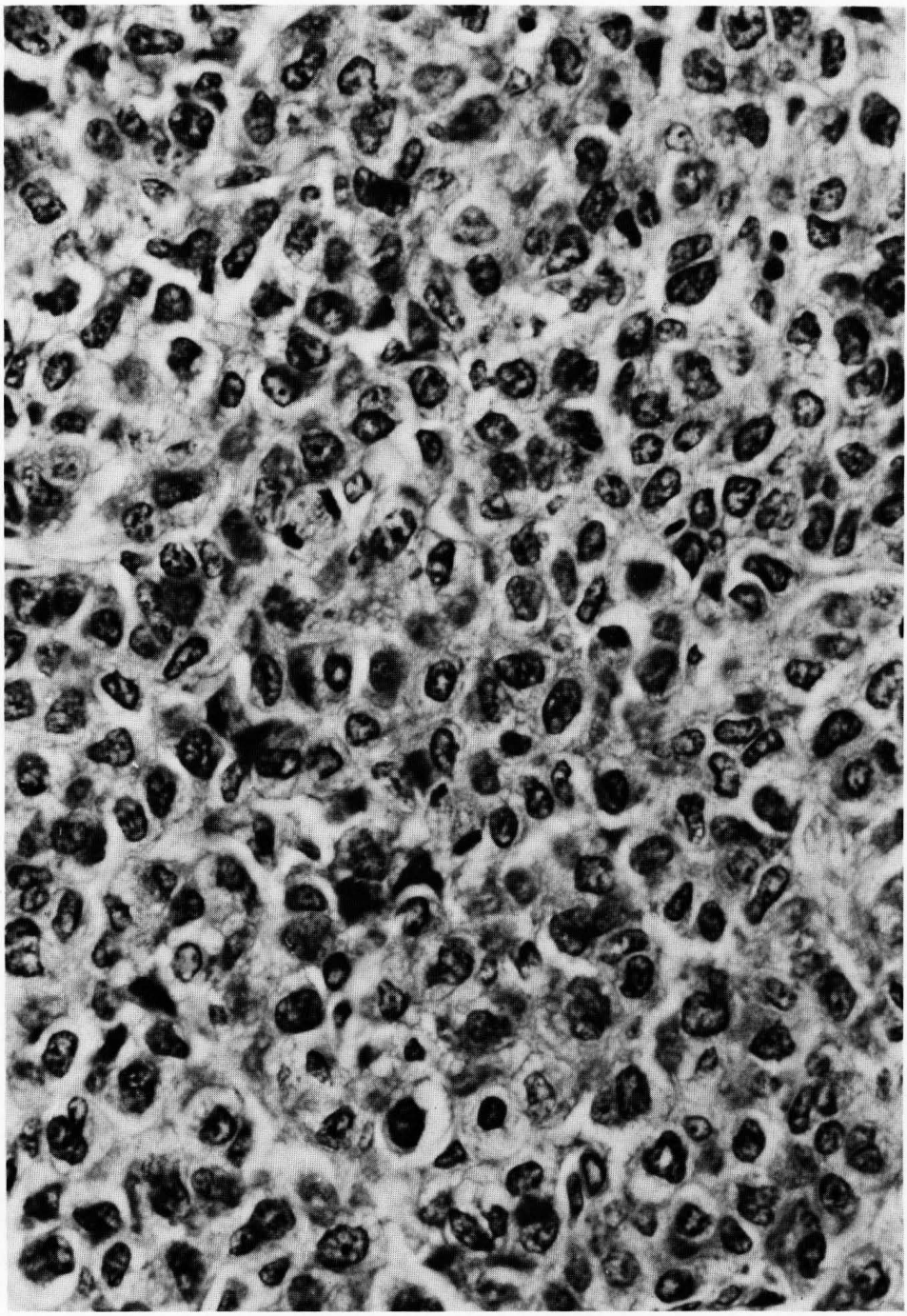

FIG. 13. Same metastasis as in Fig. 12, but higher magnification. 618×.

steel wire-meshed cages, four per cage. They were fed a semipurified diet consisting of 20% casein, 38% corn starch, 38% sucrose, 3% corn oil, and added vitamins and minerals, and supplied with ion-exchanged, glass-distilled water *ad lib.*

Two months after arrival in the laboratory, the rats in one group were each injected intratracheally with 50 μg of Be as $Be(OH)_2$ and the rats in the other group with 2.5 mg of chrysotile asbestos, a particulate control. These materials were suspended in distilled water and each rat received 0.4 cc of their respective suspensions followed by 0.2 cc of distilled water to wash the suspension from the needle. Ten months later, the $Be(OH)_2$ rats were reinjected with 25 μg of Be as $Be(OH)_2$. Twenty-five rats in the latter group were killed and autopsied at 19 months of age (6 months after the second injection). Twenty-four rats injected with chrysotile were sacrificed and autopsied at 23 months of age, 20 months after their single injection. Tissues of several organs from each rat were prepared for histologic examination by light microscopy. The description of the histopathology will be limited to the lungs. One hematoxylin and eosin-stained section of each lobe of the lungs from each rat was examined.

Cuboidal and/or columnar cell metaplasia and bronchiolar alveolar cell tumors were seen in all and squamous metaplasia in some of the rats injected with $Be(OH)_2$. In addition, 6/25 rats had pulmonary adenomas and 7/25 had adenocarcinomas. The combined incidence of adenomas and adenocarcinomas was 13/25 (52%). One rat had an epidermoid carcinoma in addition to an adenocarcinoma.

In contrast, all the animals injected with chrysotile had small scars in or near several respiratory bronchioles and occasionally larger scars which obliterated larger portions of the lungs. In two rats, adenomas appeared adjacent to the scars and, in a third rat, an adenocarcinoma occurred. There were occasional foci of cuboidal metaplasia in some of the scars, but 95% of the lungs were free from any metaplastic foci, whereas, in the lungs in 90% of the animals injected with Be, most of the normal tissue was replaced by metaplastic foci and tumors. The incidences of adenomas and adenocarcinomas in the chrysotile groups are compared with those induced by $Be(OH)_2$ in Table 2. The difference in the incidences of adenocarcinomas and the combined adenomas and adenocarcinomas between the two groups is statistically significant.

METAPLASIA AND CANCER

Epithelialization, metaplasia, and atypical proliferation of the alveolar walls have been mentioned as being precursors to the development of lung cancer in rats exposed to Be compounds (Schepers *et al.*, 1957; Schepers, 1961; Vorwald, 1950; Vorwald *et al.*, 1959; Reeves *et al.*, 1967; Wagner *et al.*, 1969). This phenomenon has also been present in all the rat experiments with Be compounds and Be ores that have been studied since 1964 by the senior author of this paper. If metaplasia were absent in the lungs of animals injected with Be compounds, no lung tumors appeared either. Although every rat with metaplasia did not have a lung tumor, the extent of metaplasia in any group of rats could be correlated with the incidence of lung cancer. All rats with Be-induced neoplasms had extensive alveolar metaplasia. Since this was such a well-documented phenomenon, short-term tests were

TABLE 2
BERYLLIUM HYDROXIDE—LUNG CANCER INCIDENCE

Tumor type	Tumor incidence			
	$Be(OH)_2$		Chrysotile	P^a
Adenoma	6/25 (24)[b]	vs	2/24 (8.3)	0.136
Adenocarcinoma	7/25 (28)	vs	1/24 (4.2)	0.028
Adenoma and adenocarcinoma	13/25 (52)	vs	3/24 (13)	0.004

[a] Fishers exact test, one-tailed. $P \leq 0.05$ indicates significant difference between groups.
[b] Percentage is shown in parentheses.

designed to compare the metaplasia-inducing capacity of several Be intermetallics with Be metal.

In the first series of experiments, respirable-sized powders of VBe_{12}, $TiBe_{12}$, $TaBe_{12}$, $NbBe_{12}$, and Be metal were tested. Eighteen-month-old female albino rats were each injected intratracheally with 0.5 mg of one of the compounds and sacrificed at intervals up to 9 months later. The experimental conditions were similar to those in the Be–alloy study. Cuboidal cell metaplasia was present in all and columnar cell and squamous cell metaplasia were present in most of the rats injected. The incidence of squamous metaplasia was 9/9 for VBe_{12}, 9/9 for Be metal, 8/10 for $TiBe_{12}$, 6/10 for $TaBe_{12}$, and 5/8 for $NbBe_{12}$. For columnar cell metaplasia, the incidence was 9/9 for VBe_{12}, 6/8 for $NbBe_{12}$, 6/10 for $TiBe_{12}$, 6/10 for $TaBe_{12}$, and 4/9 for Be metal. Although there did not appear to be a significant difference in the incidence of metaplasia, the most extensive metaplasia occurred in the VBe_{12} and Be metal rats. No malignant tumors were seen; however, bronchiolar alveolar cell tumors were present. They occurred in 4/9 rats given VBe_{12}, 2/10 with $TiBe_{12}$, 1/9 with Be metal, and 1/8 with $NbBe_{12}$. None of these lesions, except for an occasional focus of cuboidal metaplasia, was seen in 20 saline-injected control rats of the same age and strain and sacrificed at the same time.

In another similar study, respirable-sized powders of Be_4B and Be_2B (beryllium borides) and Be metal were tested. Ten rats were injected intratracheally with Be_2B, 20 with Be_4B, and 20 with Be metal. Each received a single dose equivalent to 0.5 mg of Be. Ten rats served as saline-injected controls, and experimental conditions were similar to the Be alloy study except young adult male Wistar-derived rats were used. They were all sacrificed 6 months later. Single sections of the lobes of each lung were evaluated by light microscopy. The percentage of each lung of each animal occupied by metaplastic foci was estimated and the number of squamous metaplastic foci in each lung was determined. The percentage of the area of the lung sections consisting of metaplastic foci in those groups of rats injected with Be_4B, Be_2B, and Be metal was 31, 40, and 6%, respectively. In the ten controls it was 1%. An average of 4.8 squamous metaplastic foci per lung was seen in the Be_2B group, 2.0 in the Be_4B group, 0.3 in the Be metal group, and 0.0 in the controls.

AGING EFFECT ON METAPLASIA

The following experiment was designed to determine the effect of age on the susceptibility of rats to beryllium. Three-month-old young adult and 12-month-old discard breeder Wistar-derived female rats were injected intratracheally once with

two and three different amounts of $Be(OH)_2$, respectively. Ten rats from each group were injected with 40 μg Be and ten with 4 μg Be. In addition, ten of the younger rats were each injected with 0.4 μg Be. The animals were sacrificed 6 months later. The lungs were inflated with formalin, and one section from each lobe was prepared for and examined by light microscopy. The size and number of metaplastic foci were greater in the old rats than in the young rats injected with the same amount of Be. The old rats injected with 40 μg of Be exhibited 30–50 foci (average > 30), whereas the young rats injected with the same dose had 2–20 (average 9.6) (Table 3). A similar difference was noted at the 4 μg dose (Table 3). In addition, one of the old rats injected with 40 μg Be had a pulmonary adenocarcinoma. The number of metaplastic foci with 4 μg Be in the old rats (8.5 foci/lung) was similar to the number of metaplastic foci induced with 40 μg Be in the young rats (9.6 foci/lung).

DISCUSSION

Lung cancer was induced in rat lungs with Be metal, passivated Be metal and a 60% BeAl alloy. Under the same experimental conditions other Be alloys (4% BeCu, 2.2% BeNi and 2.4% BeCuCo) containing much smaller amounts of Be failed to induce lung neoplasms in rats. This does not indicate or suggest that higher doses of these alloys under the same or different experimental conditions might not induce lung neoplasms. Further studies are indicated to determine the carcinogenic potential of those alloys.

The following compounds cause pulmonary metaplasia in rats: VBe_{12}, $TiBe_{12}$, $TaBe_{12}$, $NbBe_{12}$, Be_2B, and Be_4B. In a previous report (Stokinger, 1972), the intermetallics VBe_{12}, $TiBe_{12}$, $TaBe_{12}$, and $NbBe_{12}$ were listed as being inert because they did not produce any pulmonary tumors. However, as reported here, they are not inert. Although adenomas, adenocarcinomas, and other carcinomas were not produced, there was extensive metaplasia and a few bronchiolar alveolar cell tumors. The cellular response was sufficient to indicate that, if the compounds had been tested in higher doses for longer periods of time, cancer probably would have occurred. Also, the Be_2B and Be_4B compounds produced metaplasia equal to that of Be metal in the short-term experiment, and, therefore on a chronic carcinogenicity study they could be expected to produce cancer.

The finding of a greater number and larger areas of metaplastic foci in old rats vs

TABLE 3
PULMONARY RESPONSE TO $Be(OH)_2$ NUMBERS OF METAPLASTIC FOCI[a]

	μg Be					
	40		4		0.4	
Rats	Range	Average	Range	Average	Range	Average
Old	30–50	>30	3–18	8.5	Not done	
Young	2–20	9.6	0.10	2.8	0	

[a] Ten rats in each group.

young adult rats receiving the same dose of $Be(OH)_2$ suggests that older animals might be more susceptible to the induction of lung cancer by beryllium. In support of this are the epidemiologic findings by Mancuso (1970). In a retrospective study on workers in the beryllium industry, he found that the men with the highest lung cancer rates were between 38 and 65 years of age at the time of their first exposure. In addition, these men were exposed for very short periods of time, and several had clinically diagnosed pneumonitis, possibly chemical, indicating a short-term, high-dose exposure, not unlike injecting rats intratracheally one time and inducing cancer.

This effect of age on the susceptibility to the development of cancer might also apply to other agents. Curry *et al.* (1975) reported that of 123 cases of hepatic malignancies induced by the intravenous injection of thorotrast, all occurred in people between the ages of 49 and 55, regardless of age at the time of injection. The latent periods varied from 3 to 35 years.

Beryllium is the most potent inorganic pulmonary carcinogen that has been tested in animals. As little as 35μg Be/m^3 as $BeSO_4$ for 6 months of intermittent inhalation exposure induced cancer in 58% of rats (Schepers, 1957). Exposures of the same concentration of $BeSO_4$ for 13 months caused cancer in 100% of rats (Reeves *et al.*, 1967). Inhalation exposures to as little as 2.8 μg Be/m^3 were stated by Vorwald *et al.* (1966) to have caused lung cancer. For purposes of comparison, it should be noted that 78 weeks of inhalation exposures to 1000 μg of nickel sulfide/m^3 were required to induce lung cancer in only 5–7% of the rats, and lung neoplasms (including cancer) in 14% (Ottolenghi *et al.*, 1974). Also, intratracheal injections of a total of 75 μg Be as $Be(OH)_2$ per rat caused lung tumors in 52% of the animals, whereas 2500 μg of chrysotile produced lung tumors in only 13% of the rats as reported in this paper.

Because beryllium is a potent carcinogen in animals, one might expect a high incidence of lung cancer in workers in the beryllium production industries. There is evidence now that these workers have a higher risk for developing lung cancer than the general population (Mancuso, 1970; Wagoner *et al.*, 1980; Infante *et al.*, 1980). The question is, however, why isn't that risk greater? There are several possibilities. In general, most of the beryllium production workers were employed for only short periods of time. For instance, in the period 1940–1949, 84.3% of beryllium production workers were employed in one beryllium production facility for less than 3 years, and 70% were employed for less than 1 year (Wagoner *et al.*, 1980). The fact that an excess of lung cancer was demonstrable at all with that short an exposure is probably a reflection of the extremely high concentrations of airborne Be. Concentrations as high as 4710 μg/m^3 were measured during pouring operations (Laskin *et al.*, 1950). Another indication of the high airborne concentrations of beryllium is the incidence of acute pneumonitis in that time period (Preuss, 1977). For example, in 1943, approximately 50% of the yearly average workforce in one beryllium production facility developed acute pneumonitis (Preuss, 1977). This condition has been only infrequently observed since 1950.

Another possibility is that industrial hygiene practices were initiated in 1949 to reduce the airborne Be concentrations to 2 μg/m^3 (AEC method), which is equivalent to about 0.5 μg respirable Be/m^3 (Donaldson, 1973). If these levels were in fact obtained, one might be able to equate the lack of very high lung cancer risk to

better engineering controls. However, Donaldson (1973) found mean respirable Be concentrations in 1968 and 1970 for several job categories ranging from 0.15 to 5.64 μg Be/m^3, and individual mean values as high as 38 μg Be/m^3. Many of these levels would certainly be adequqte to produce lung cancer in animals. The final possibility is that the men were probably not frequently inhaling those high concentrations because they wore supplied air respirators (Donaldson, 1973). In fact, there are no data which show how much Be the men were actually inhaling. If the latter reason explains the lack of very high demonstrable lung cancer risk, then it is extremely important that this be documented, since there probably are other Be exposures occurring where supplied air respirators are not worn, e.g., in welding and in foundries.

All of the above are possible explanations for the relatively greater carcinogenic response of exposed animals to beryllium as compared to the carcinogenic response observed among Be-exposed workers. There should be no need to speculate that animals are different from humans with regard to their response to beryllium. In fact, Schepers (1955) pointed out that the early changes seen in lungs of rats exposed to beryllium were also present in most of the lungs from people exposed to beryllium, including the epithelialization of alveolar walls, a "premalignant" lesion in rats.

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