- Martin, A. R. (1939). *Amer. J. Orthopsychiat.*, **9**, 123.
 Miller, R., and Slavson, S. (1939). *Ibid.*, **9**, 79.
 Ozertsovsky, D. S. (1927). *Zh. Neupatol. Psikhiat.*, **20**, 587.
 Pratt, J. H. (1907). *J. Amer. med. Ass.*, **49**, 755.
 — (1907). *Medical Communications of the Massachusetts Medical Society*, **20**, 475.
 — (1911). *Trans. Amer. climat. Ass.*, **27**, 87.
 — (1922). *Hosp. soc. Serv.*, **6**, 401.
 — (1934). *Int. Clin. Series*, **44s**, **4**, 1.
 Rees, J. R. (1935). *Proc. roy. Soc. Med.*, **28**, 1229.
 Reik, T. (1929). *Int. J. Psycho-anal.*, **10**, 292.
 Ross, E. A. (1919). *Social Psychology*, Macmillan, New York.
 Schilder, P. (1939). *Ment. Hyg.*, **23**, 87.
 Slavson, S. R. (1940). *Ibid.*, **24**, 36.
 Smith, G. B. (1927). *J. Amer. med. Ass.*, **89**, 1949.
 Smith, L. H. (1933). *Amer. J. Psychol.*, **13**, 33.
 Snowden, E. N. (1940). *Lancet*, **2**, 769.
 Sommers, M. R., and Pouppirt, P. S. (1940). *Calif. West. Med.*, **53**, 79.
 Wender, L. (1936). *J. nerv. ment. Dis.*, **84**, 54.
 — (1940). *Psychiat. Quart.*, **14**, 708.
 Wittels, Fritz (1939). *Amer. J. Sociol.*, **45**, 433.

LUNG TUMOURS IN MICE

INCIDENCE AS AFFECTED BY INHALATION OF CERTAIN CARCINOGENIC AGENTS AND SOME DUSTS

BY

J. ARGYLL CAMPBELL, M.D., D.Sc.

(From the National Institute for Medical Research, London)

In previous researches (Campbell, 1934, 1937a, 1937b, 1940) it was demonstrated that the incidence of primary lung tumours in mice may be increased by the inhalation either of tarred road dust, both with the tar and after its extraction, or of brown oxide of iron or precipitated silica, the effect being most pronounced with the tarred road dust containing tar. In continuation of these studies with the intention of seeking for stimulators or inhibitors of lung tumours, the effects of the following have been tested, and the results are given herein: (a) precipitated silica containing methylcholanthrene; (b) steel grindings; (c) a mixture containing equal parts of alumina, precipitated silica, and brown oxide of iron; (d) a radio-active dust from Czechoslovakia; (e) a mixture containing the same three substances as c plus calcium carbonate; (f) a further sample of tarred road dust.

Methods

The technique employed was similar to that used in the researches cited above. For each experiment 150 mice were used—75 mice, half of each sex, for the dusted group, and 75 for the controls. Equal numbers of mice of the same colour were placed in the experimental and control groups. The mice were 3 months old, and were obtained from the mixed stock of this institute. The sexes were kept separate, and the mice placed in boxes containing eight to ten animals. The dusted mice were exposed in a closed chamber to a moderate cloud of dust once an hour for six times a day on five days each week for a year. They were allowed to complete their allotted span of life. Histological sections were made of all lungs and tracheo-bronchial lymph glands and of any organ showing pathological change.

Results from Silica plus Methylcholanthrene

The silica (British Drug Houses) was precipitated from sodium silicate by nitric acid, and was the same as that used in some of the previous experiments (Campbell, 1940, 1941). It was proved by x-ray analysis at the National Physical Laboratory to be amorphous and therefore without the crystal unit characteristic of quartz. During each day of dusting each box of eight to ten mice received about 500 mg. of silica dust containing 0.8 mg. of finely divided methylcholanthrene. At the beginning of the experiment a small amount of cholanthrene was also present. There is no way to determine accurately the amount of the carcinogenic agent inhaled by each mouse over the whole year of dusting, but the total quantity of methylcholanthrene entering each box of mice was about 200 mg. for the whole year. The majority of the particles and clumps of particles of silica in the cloud measured less than 5 μ .

The dusting produced primary lung tumours in 15 (23.8%) of the 63 mice living 10 months or longer compared with 9 (13.6%) of the 66 similar control mice (Control I)—that is, the incidence is nearly doubled (Tables I and II). One of the tumours in a control mouse had an extension in the tracheo-bronchial lymph glands. Mice younger than 10 months very rarely show lung tumours, and have therefore been excluded from the calculations. There is no doubt that, in mice, age is a factor in the development of pulmonary tumours. In the 15 dusted mice with tumours 8 had single tumours, 6 had two tumours, and 1 mouse had three tumours in the lungs. These numbers are few compared with those of some former experiments, and there is also a diminution in surface (pleural) area and in malignancy. On the average, in the present experiments the surface area of each tumour was only about 3.5 sq. mm., the largest tumour being 25 sq. mm. The tumours of the control group were also few in number and small in size compared with some former controls, and it is apparent that our stock of mice has recently become more resistant to development of pulmonary or any other tumours. Although the incidence of lung tumours was doubled by the dusting, a much greater effect was expected because methylcholanthrene is one of the most potent carcinogenic agents (Twort and Twort, 1939; Iball, 1939), and some previous observers have obtained marked increases in the incidence of pulmonary tumours by apparently very small quantities of methylcholanthrene injected subcutaneously (Andervont, 1939; Grady and Stewart, 1939), administered by mouth (Magnus, 1939; Lorenz and Stewart, 1940), or injected direct into the trachea (Shimkin, 1939). In the present investigation the increase observed was of a degree to be expected by dusting with silica alone (Campbell, 1940), and it is possible that the added methylcholanthrene was present in too small a quantity or had become adsorbed to the silica particles, thus being rendered harmless. Charcoal has been found to act in this way and to hold the carcinogenic agent at the site of injection (Andervont and Lorenz, 1937); there is evidence also that in inhalation experiments carbon has an inhibitory effect (Campbell, 1939). It must be remembered, too, that different strains of mice reveal wide differences in tendency to lung tumours. For some unknown reason the mixed strain of this institute appears to have recently become more resistant in this respect. Such changes may explain why some observers have failed to produce lung tumours by direct insufflation of carcinogenic agents into the air passages (Oberling *et al.*, 1936, with 3:4-benzpyrene; Burrows, quoted by Cook *et al.*, 1937, with 1:2:5:6-dibenzanthracene). There is no doubt that by inbreeding of mice it is possible to produce strains either very susceptible or very resistant to production of lung tumours, and in this respect heredity plays a major part.

Results from Steel Grindings

This experiment was undertaken because there is evidence of a relatively high incidence of carcinoma of the lung in metal grinders, engineers, and foundry workers (Kennaway and Kennaway, 1936; Turner and Grace, 1938), and also because dusting with brown oxide of iron increases the incidence of primary lung tumours in mice (Campbell, 1940).

The steel grindings were obtained by grinding down cast-steel files—made of high-carbon-content steel—on a corundum grinding wheel. The filings were passed through a 100-mesh filter, and the majority of the particles in the dust cloud from the resulting powder measured less than 5 μ . Analysis indicated that more than 75% of the dust entering the chamber was iron. There was also a certain

amount of substance from the corundum wheel. The particles were heavy, and every day about 3.5 grammes of dust entered each box, containing eight to ten mice. Certainly some of the very small steel particles remained long enough in the cloud of dust to be inhaled by the mice, since steel particles were present in the lung tissue, damaging the cutting edge of the knife used for section. Microscopical examination indicated that the lungs (Table III) of the majority of the animals contained only a moderate deposit of dust, as did the tracheo-bronchial lymph glands (Table IV), although a few of these glands had heavy deposits. These data for the degree of dusting give a general indication of the condition; since several sections of tissue were examined in each case; but, as serial sections of the entire lungs and glands were not made, the details in Tables III and IV are approximate only.

Among the mice exposed to the steel grindings there were 59 which lived for 10 months or longer, and of these 8 (13.6%) possessed lung tumours, compared with 4 (7.7%) of 52 control mice (Tables I and II). Half of the tumours in each group were malignant, and in one of the dusted mice the tumour gave rise to an extension in the tracheo-bronchial lymph glands. The dusting therefore produced some increase in the incidence of lung tumours, but this was not so great as with the brown oxide of iron (Campbell, 1940), and with the latter the tumours also showed a greater malignancy.

Results from Alumina plus Silica plus Brown Oxide of Iron

Experiments of this type were performed to determine whether certain substances—e.g., aluminium—exhibit an inhibitory effect on development of lung tumours, as has been recorded and confirmed for silicosis (Denny *et al.*, 1937; Naeslund, 1940). The substances (British Drug Houses) were well mixed together in equal proportions, and each day about 500 mg. of the mixture entered each box containing eight to ten mice. Some indication of the degree of dusting was obtained from the deposit of brown oxide of iron as observed by microscopical examination of the lungs, but the alumina and silica could not be seen. The deposit of iron oxide in the lungs was moderate to slight in most mice (Table III), so that the dusting with all three dusts must have been heavy, although some of it may have been absorbed. The tracheo-bronchial lymph glands showed a slight deposit of iron oxide, but of course with the other two dusts the total must have been three times as great, or at any rate considerable. In some cases the silica gave evidence of its presence in the glands by producing fibrotic nodules (Table V). The dusting produced only a slight increase in the incidence of the lung tumours of the mice living 10 months or longer. Thus 9 (15.8%) of the 57 dusted mice and 6 (9.2%) of the 65 control mice possessed lung tumours (Tables I and II); in one of the dusted mice there was an extension into the tracheo-bronchial lymph glands. It is possible that the alumina may have somewhat retarded the action of the silica and iron (Campbell, 1940) in stimulating the growth of the lung tumours, but here again it must be remembered that the control mice appear to have become less sensitive to the growth of tumours.

Results from Radio-active Czechoslovak Dust

In a former research (Campbell, 1940) a dust from the vicinity of the Joachimsthal mine, where the incidence of human lung cancer is high, was tested on mice, and it produced some increase over the controls in incidence of lung tumours. This first sample of dust, however, was

not obtained from the active ore of the mines, and therefore did not contain the essentially active products in any quantity. Through the courtesy of Prof. J. Löwy a small amount of the active dust was obtained. This active dust is said to contain usually up to 55% of uranium, 2% of arsenic, and some radium. The sample kindly presented by Prof. Löwy was analysed at the Government Laboratory, London, and was found to contain 53.6% of uranium (as U), 0.6% of arsenic (as As), and radium (as Ra) 0.016 mg. per 100 grammes, equivalent to 160 mg. per ton.

As I did not have very much of this active sample, and as I wished to avoid poisoning with arsenic, the dust was diluted in the proportion of 1 gramme to 20 grammes with the previous and much less radio-active sample of Joachimsthal dust. Every day about 750 mg. of this mixture entered each mouse-box. The deposit of the dust in the lungs was, however, mainly slight to moderate (Table III), but there was in some cases a very heavy deposit in the tracheo-bronchial lymph glands (Table IV). These lymph glands rather surprisingly did not show any pathological change beyond hyperplasia, such as is produced by most dusts not containing carcinogenic agents.

As regards lung tumours there appeared to be a definite increase in incidence in the 64 dusted mice living 10 months or longer, 13 (20.3%) of them having tumours, 8 of which were malignant, while only 1 (2.1%) of the 47 control mice had a tumour, and this a simple one (Tables I and II). The increase, therefore, is tenfold—similar to that with the less active sample (Campbell, 1940); I expected to find more mice with tumours with the more active dust, so that it is possible it had been diluted too much. At the same time I carried out an experiment exposing 20 mice, ten in each of two cages containing a small dish (diameter 6 cm., depth 1 cm.) of the active undiluted dust, so that the animals were continually exposed to the radiation. Half of the mice lived from about 500 to 700 days, and were exposed to the radiations for from 400 to 600 days, yet none of them developed tumours of any organ. The dust was not stirred up inside the cage, and was separated from the mice only by thin wire mesh.

Results from Alumina plus Silica plus Brown Iron Oxide plus Calcium Carbonate

These substances (British Drug Houses) were mixed together in equal proportions, and each day about 500 mg. of the mixture entered each box of eight to ten mice, the particles and clumps of particles of the dust cloud produced being mostly less than 5μ in diameter. There was no evidence of an inhibitory action by the alumina or calcium carbonate, since there was a definite increase in incidence of lung tumours—12 (19.4%) of the 62 dusted mice living 10 months or longer—and none of the 60 control mice revealed such tumours; 7 of the 12 tumours in the dusted mice were malignant. The deposit of dust in the lungs, in this instance the brown oxide of iron alone, was in most mice moderate to heavy (Table III), so that with the other three dusts there must originally have been very heavy deposits, some of which no doubt was removed by absorption. The tracheo-bronchial lymph glands in most mice contained slight to moderate deposits of iron oxide (Table IV), and the silica revealed its presence in some cases by producing marked fibrotic nodules (Table V).

Results from Tarred Road Dust

In the first experiment with tarred road dust (Campbell, 1934) a ninefold increase in incidence of lung tumours of mice was produced and at the same time most of the dusted mice developed typical cancer of the skin, although the dust was not rubbed into the skin except by the mice themselves.

TABLE I.—Synopsis of Pathological Data

Group of Mice	No. of Mice		Mice over 10 Months with Pulmonary Tumours	Mice with Mammary Tumours	Mice (All Ages) with Increase of Lymph Tissue			Mice with Pneumonias
	Original	Living 10 Months or Longer			Bronchial Nodes	Lungs	"General"	
Control I	75	66	9 (13.6%)	0	6 (8.0%)	10 (13.3%)	2 (2.7%)	9 (12.0%)
" II	72	52	4 (7.7%)	4	14 (19.4%)	3 (4.1%)	3 (4.1%)	5 (6.9%)
" III	73	65	6 (9.2%)	0	14 (19.1%)	1 (1.4%)	2 (2.7%)	6 (8.2%)
" IV	72	47	1 (2.1%)	0	10 (13.9%)	3 (4.1%)	1 (1.4%)	10 (13.9%)
" V	76	60	0 (0.0%)	0	7 (9.2%)	0 (0.0%)	0 (0.0%)	5 (6.6%)
" VI	76	69	1 (1.4%)	0	12 (15.8%)	3 (3.9%)	0 (0.0%)	18 (23.7%)
Totals	444	359	21 (5.8%)	4	63 (14.2%)	20 (4.5%)	8 (1.8%)	53 (11.9%)
SiO ₂ + MeChol.	76	63	15 (23.8%)	0	18 (23.7%)	14 (18.4%)	2 (2.6%)	23 (30.3%)
Steel grindings	75	59	8 (13.6%)	1	33 (44.0%)	19 (25.3%)	1 (1.3%)	19 (25.3%)
Al ₂ O ₃ + SiO ₂ + Fe ₂ O ₃	75	57	9 (15.8%)	0	39 (52.0%)	18 (24.0%)	3 (4.0%)	21 (28.0%)
Czechoslovak dust (2)	74	64	13 (20.3%)	1	26 (35.1%)	9 (12.1%)	2 (2.7%)	16 (21.6%)
Al ₂ O ₃ + SiO ₂ + Fe ₂ O ₃ + CaCO ₃	77	62	12 (19.4%)	0	31 (40.3%)	12 (15.6%)	3 (3.9%)	15 (19.4%)
Tarred road dust (2)	76	61	8 (13.1%)	0	33 (43.4%)	6 (7.9%)	0 (0.0%)	18 (23.7%)
Totals	453	366	65 (17.7%)	2	180 (39.7%)	78 (17.2%)	11 (2.4%)	112 (24.7%)

TABLE II.—Total Numbers of Lung Tumours in Mice living 10 Months or Longer

Experiment	Length of Experiment from 1st Day of Dusting (Days)	No. of Mice		Animals with Lung Tumours					
		Control	Dusted	Control			Dusted		
				Total	Simple	Malignant	Total	Simple	Malignant
SiO ₂ + MeChol.	710	66	63	9	5	4	15	11	4
Steel grindings	766	52	59	4	2	2	8	4	4
Al ₂ O ₃ + SiO ₂ + Fe ₂ O ₃	838	65	57	6	3	3	9	6	3
Czechoslovak dust (2)	870	47	64	1	0	0	13	5	8
Al ₂ O ₃ + SiO ₂ + Fe ₂ O ₃ + CaCO ₃	708	60	62	0	0	0	12	5	7
Tarred road dust (2)	661	69	61	1	0	1	8	4	4
Totals	—	359	366	21 (5.8%)	11 (3.0%)	10 (2.8%)	65 (17.7%)	35 (9.5%)	30 (8.2%)

TABLE III.—Degree of Dusting. Deposit in Lungs of Mice of All Ages

Experiment	No. of Mice with Deposit in Lungs								No. of Mice	
	Very Slight	Slight	Slight to Moderate	Moderate	Moderate to Heavy	Heavy	Heavy to Very Heavy	Very Heavy	With Dust	Still Alive after First Clear Evidence of Deposit
Steel grindings	3	5	8	22	19	4	0	0	61	64
(Al ₂ O ₃ + SiO ₂) + Fe ₂ O ₃	4	12	35	10	1	0	0	0	62	62
Czechoslovak dust (2)	3	27	12	12	5	0	0	0	59	61
(Al ₂ O ₃ + SiO ₂ + CaCO ₃) + Fe ₂ O ₃	4	5	10	32	11	0	0	0	62	65
Tarred road dust (2)	6	12	20	17	9	1	0	0	65	66
(SiO ₂) + Fe ₂ O ₃ (1940)	2	14	24	18	1	0	0	0	59	62

TABLE IV.—Degree of Dusting. Deposit in Tracheo-bronchial Lymph Glands of Mice of All Ages

Experiment	No. of Mice with Deposit in Glands								No. of Mice	
	Very Slight	Slight	Slight to Moderate	Moderate	Moderate to Heavy	Heavy	Heavy to Very Heavy	Very Heavy	With Dust	Still Alive after First Clear Evidence of Deposit
Steel grindings	3	12	3	9	3	3	0	0	33	49
(Al ₂ O ₃ + SiO ₂) + Fe ₂ O ₃	7	21	3	1	1	0	0	0	33	45
Czechoslovak dust (2)	3	4	9	5	5	0	3	13	42	54
(Al ₂ O ₃ + SiO ₂ + CaCO ₃) + Fe ₂ O ₃	5	21	3	6	1	0	0	0	36	51
Tarred road dust (2)	2	4	1	3	11	5	4	7	37	58
(SiO ₂) + Fe ₂ O ₃ (1940)	5	17	1	3	1	0	0	0	27	46

TABLE V.—Fibrotic Nodules in Tracheo-bronchial Lymph Glands, produced by Amorphous SiO₂

Experiment	No. of Mice		No. with Fibrotic Nodules					First Evidence	
	Original	Living 10 Months or Longer	Total	Well Marked	Marked	Slight	Very Slight	Days after First Day of Dusting	Age of Mouse (Days)
SiO ₂ (1940)	75	61	41	8	18	12	3	174	264
SiO ₂ + Fe ₂ O ₃ (1940)	74	62	5	0	0	3	2	465	555
SiO ₂ + MeChol.	76	63	32	5	12	13	2	266	356
SiO ₂ + Fe ₂ O ₃ + A ₂ O ₃	75	57	18	0	2	11	5	270	360
SiO ₂ + Fe ₂ O ₃ + Al ₂ O ₃ + CaCO ₃	77	62	23	0	7	7	9	273	363
Totals	377	305	119	13	39	46	21	—	—

TABLE VI.—Lung Tumours in Mice living 23 Months or Longer

Experiment	Control Mice			Dusted Mice				
	No.	Mice with Tumours			No.	Mice with Tumours		
		Total	Simple	Malignant		Total	Simple	Malignant
SiO ₂ + MeChol.	19	5	2	3	13	9	7	2
Steel grindings	17	2	1	1	8	3	1	2
Al ₂ O ₃ + SiO ₂ + Fe ₂ O ₃	16	4	1	3	14	4	3	3
Czechoslovak dust (2)	6	0	0	0	18	7	5	2
Al ₂ O ₃ + SiO ₂ + Fe ₂ O ₃ + CaCO ₃	4	0	0	0	13	3	2	1
Tarred road dust (2)	8	0	0	0	11	4	1	3
Totals	70	11 (15.7%)	4 (5.7%)	7 (10.0%)	77	30 (38.9%)	17 (22.0%)	13 (16.9%)

Obviously a very active carcinogenic agent was present, and there is no doubt about the result, since others have obtained similar great numbers of tumours by means of carcinogenic agents, sometimes used in very small quantity. In a further experiment (Campbell, 1937a) the tar was removed from the dust by benzene, yet the tar-free dust still produced an increase in incidence and in malignancy of lung tumours, although the rise in incidence was less than when the tar was also present. The inorganic constituents of the dust have been proved to be partly responsible for the increase in lung tumours, but a carcinogenic agent which the benzene failed to remove may still have been included.

The present sample of tarred road dust was obtained from the same road surface as the above sample, but about five years after the tarring had been done, whereas the former sample was obtained soon after tarring. The present sample of dust still contains about 2% of tar, but the carcinogenic agent, although still there, is not so active as in the former sample, since the dust did not produce cancer of the skin by the dusting alone. Also, when tested by the mouse skin test—that is, by bi-weekly tarring of the skin with the tar extracted from the dust by benzene—this second sample was not so powerful as the previous one, it being possible that the longer exposure on the road surface to light and air may have weakened the carcinogenic agent. The inorganic constituents of the second sample are similar to those of the previous one (Campbell, 1934, 1937a).

In the present case the dusting produced about a ninefold increase in lung tumours, there being 8 (13.1%) of the 61 dusted mice and 1 (1.4%) of the 69 control mice with tumours (Tables I and II). In the former experiment the increase was also about ninefold, but this was much more impressive than the present increase, since the figures for incidence of lung tumours in the former were 74% for the dusted mice and 8% for the controls—that is, many more of the mice had lung tumours in the former experiment.

In the present experiment the deposit of dust in the lungs of most of the dusted mice was of moderate amount (Table III), but some of the lymph glands contained very heavy deposits (Table IV), yet they showed only hyperplasia of lymph tissue (Table I) as occurs both in the lungs and in the glands of mice exposed to dust not containing carcinogenic agents.

Conclusions

Lung Tumours.—All the dusts tested herein produced some increase in incidence of primary lung tumours of mice living 10 months or longer, the Czechoslovak dust, tarred road dust, and the mixture containing alumina, silica, iron oxide, and calcium carbonate showing the greater increases. In some cases, however, the results were not so impressive as had been expected. Recently the stock of mice seems to have become more resistant to development of tumours. In the control groups of a total of 359 mice about 7% possessed tumours of any kind, and practically all these tumours were of the lung. In a previous group of 593 control mice the incidence of tumours of all kinds was about 12% (Campbell, 1940), nearly twice that of the present group, and again nearly all these tumours were in the lung. The incidence of all kinds of cancer in man is about 10%, and lung tumours, although increasing recently in numbers, are fewer than those of the alimentary and reproductive systems. It is possible that if there were inbreeding in man lung tumours might increase to a much greater extent in certain groups, as occurs with certain strains of mice. The high incidence of lung cancer in Czechoslovak mining districts may be influenced by some such factor of heredity. Radium under certain circumstances reduces tumour growth, and it is curious that this inhibitory action should

not be more apparent in the human lung tumours in Czechoslovakia: radium may not be the only factor concerned.

As indicated in Tables I and II the increase in incidence of lung tumours in all the dusted groups of mice living 10 months or longer (total 366) is threefold that of the controls (total 359). A similar result is obtained if the mice living 23 months or longer (70 controls; 77 dusted) are alone considered (Table VI). In both controls and dusted mice the older mice have the higher incidence.

In all there were 86 mice with lung tumours, and 64% of these were in females and 36% in males; in man, lung tumours are more prevalent in the male. As regards colour, of the total 897 mice 295 were white, 260 fawn, and 217 chocolate; 13.9% of the white mice, 10% of the fawn, and 6.4% of the chocolate had lung tumours.

Lymph Tissue.—There was nearly a fourfold increase in the incidence of hyperplasia of lymph tissue of the lung and a threefold increase for the tracheo-bronchial lymph glands as the result of the dusting (Table I). The types of cells concerned in this reticulosis were sometimes the lymphocytes chiefly and sometimes the reticulum cells, and again sometimes both more or less equally. In previous dusting experiments a similar and expected reticulosis was observed (Campbell, 1940). Normally the tracheo-bronchial lymph nodes of the mouse are about two in number and about 1 to 2 mm. in diameter. Hyperplasia was considered to be present if this diameter was increased to 3 mm. or more. Sometimes the increase was very marked. Reticulosis of other organs ("General," Table I) was not affected by the dusting.

Pneumonias.—With the exception of Control Group VI (Table I), the dusted mice revealed a much higher incidence of pneumonia and bronchopneumonia taken together than did the control mice.

Silicotic Nodules.—So far as I know, the production of silicotic nodules by an amorphous silica, not containing the crystal unit of quartz, has not been demonstrated in any other laboratory; the present results for the tracheo-bronchial lymph glands confirm the original findings (Campbell, 1940, 1941). All the results (including those of 1940) obtained with this silica are recorded in Table V. Silicotic nodules were not produced in the lungs themselves, probably because most of the silica had been removed from the lungs, the degree of dusting not being heavy enough to affect them also. An experiment with much heavier dusting is now being conducted. As expected, the experiments (Table V) with silica alone and with silica plus the very small quantity of methylcholanthrene produced the greatest numbers and most pronounced fibrotic nodules in the lymph glands. The first nodules must have appeared in less than six months. In the other three experiments the silica was diluted by other dusts, so that the effect was not so obvious. In the experiment with silica plus iron oxide the result was less marked than expected, and it is possible that the iron oxide inhibited the development of silicosis, since some other, but not all, observers report a similar inhibitory action for iron oxide (Naeslund, 1940). It would appear that, taking account of the dilution of the silica, neither alumina nor calcium carbonate exerted any active inhibition of silicosis in the lymph glands of mice under the existing conditions. The crucial experiment with aluminium and silica only is now being conducted. The original discovery by Canadian workers (Denny *et al.*, 1937) of such an inhibitory action of aluminium in the case of silicosis of the rabbit's lung has been confirmed (Naeslund, 1940).

Summary

All six dusts or mixtures of dusts tested herein increased the incidence of primary lung tumours in mice: in all experiments taken together the increase in mice living ten months or

longer was threefold that for controls. Certain of the increases were not so impressive as expected. Some of these dusts (Czechoslovak, tarred road, silica, iron oxide) are under suspicion as causes of lung tumours in man.

Heredity, age, the so-called carcinogenic agents, and some dusts are definite factors in the experimental development of lung tumours in mice. Efforts to inhibit lung tumours with alumina or calcium carbonate were unsuccessful.

The dusts produced about a fourfold increase in the incidence of hyperplasia of lymph tissue in the lungs and a threefold increase for tracheo-bronchial lymph glands. There was also an increase in most experiments in the incidence of the pneumonias.

Silicotic nodules were produced in the tracheo-bronchial lymph glands of mice breathing an amorphous silica; this confirms the first (Campbell, 1940, 1941) demonstration of silicosis produced without the crystal unit of quartz.

I am indebted to Prof. J. Löwy for the active sample of Czechoslovak dust; to my colleague Dr. H. King's department for some advice and help with certain of the analyses; to Mr. C. Pergande for technical assistance in this research; and to Mr. F. J. Higginson for cutting and staining the sections.

REFERENCES

- Andervont, H. B. (1939). *Publ. Hlth. Rep., Wash.*, **54**, 1158.
 — and Lorenz, E. (1937). *Ibid.*, **52**, 1931.
 Campbell, J. Argyll (1934). *Brit. J. exp. Path.*, **15**, 287.
 — (1937a). *Ibid.*, **18**, 215.
 — (1937b). *J. industr. Hyg.*, **19**, 449.
 — (1939). *Brit. J. exp. Path.*, **20**, 122.
 — (1940). *British Medical Journal*, **2**, 275.
 — (1941). *Brit. J. exp. Path.*, **22**, 76.
 Cook, J. W., Haslewood, G. A. D., Hewett, C. L., Hieger, I., Kennaway, E. L., and Mayneord, W. V. (1937). *Amer. J. Cancer*, **20**, 219.
 Denny, J. J., Robson, W. D., and Irwin, D. A. (1937). *Canad. med. Ass. J.*, **37**, 1.
 Grady, H. G., and Stewart, H. L. (1939). *Amer. J. Path.*, **15**, 615.
 Iball, J. (1939). *Amer. J. Cancer*, **35**, 188.
 Kennaway, N. M., and Kennaway, E. L. (1936). *J. Hyg., Camb.*, **36**, 236.
 Lorenz, E., and Stewart, H. L. (1940). *J. nat. Cancer Inst.*, **1**, 17.
 Magnus, H. A. (1939). *J. Path. Bact.*, **49**, 21.
 Naeslund, C. (1940). *J. industr. Hyg.*, **22**, 1.
 Oberling, C. H., Sannicé, C., and Guérin, M. and P. (1936). *Bull. Ass. franc. Cancer*, **25**, 156.
 Shimkin, M. B. (1939). *Amer. J. Cancer*, **35**, 538.
 Turner, H. M., and Grace, H. G. (1938). *J. Hyg., Camb.*, **38**, 90.
 Twort, J. M., and Twort, C. C. (1939). *Amer. J. Cancer*, **35**, 80.

ISOLATED FRACTURE OF THE CARPAL CUNEIFORM

BY

W. P. GREENING, F.R.C.S.

Surgical Registrar, Charing Cross Hospital

During the past two years 580 cases of injuries to the wrist have been seen at this hospital, and 20 of these have been fractures of the carpal cuneiform. The condition has been referred to by Kellogg Speed (1925), and an article by F. Deneke (1911) included the bibliography up to that date. The latter author described 3 cases, in each of which there was a fracture of the styloid process of the ulna.

Aetiology.—The condition arises as a result of a fall on the outstretched hand. Of the 20 cases seen at this hospital none was due to direct injury, and 3 had an associated fracture of the lower end of the radius. The observations by previous writers, including Kellogg Speed, that isolated fracture of the cuneiform is a rare condition do not, therefore, appear to be accurate.

Physical Signs.—The patient complains of pain over the ulnar aspect of the dorsum of the wrist. All movements are painful, particularly ulnar deviation. There is always considerable swelling, and a localized point of tenderness can be felt directly over the cuneiform.

X-ray Appearances.—No abnormality will be present in the antero-posterior view unless there is an associated fracture of the proximal row of carpal bones or of the lower end of the radius or ulna. In the lateral view three clearly

defined types of fracture may be recognized: (1) an area extending through two-thirds of the cuneiform at its dorsal aspect, with radiating cracks or fissures through the bone; (2) a small flake of bone avulsed from the dorsum with considerable separation; and (3) a small flake fracture with no separation.

Pathology.—In those cases in which the injury was sustained by a fall on the palm of the outstretched hand a fairly large area of the dorsum of the cuneiform was fractured, for in the dorsiflexed position the cuneiform is compressed between the pisiform and the lower end of the ulna, giving rise to a typical fracture extending through the bone. Radiographs taken in dorsiflexion show the situation of these bones in relation one to another (Fig. 1). The force may, however, be so applied that the cuneiform is momentarily dislocated backwards, and the strong ligaments passing between it and the semilunar avulse a flake of bone without an associated compression fracture. Case 2 illustrates this point. A radiograph showed not only a small flake fracture of the cuneiform but also a posterior marginal fracture of the lower end of the radius, a condition caused only by a fall on the outstretched palm. This patient located the tenderness not on the ulnar collateral ligament but between the cuneiform and the semilunar. When, however, the patient falls on to the back of the hand, only small flake fractures of the cuneiform are seen in the

FIG. 1.—Radiograph showing wrist in dorsiflexion. It will be seen that a fall on the wrist in that position compresses the cuneiform between the pisiform and the lower end of the ulna.

radiograph. When the wrist is violently plantar-flexed the ulnar collateral ligament is strained, and either a flake of bone is removed from the cuneiform or the ligament itself is torn. It has been observed, also, that a fracture of the cuneiform always accompanies a perilunar dislocation of the carpus, where all the bones of the wrist, with the exception of the semilunar, are dislocated backwards and outwards, and as a result flakes of bone are torn from the cuneiform by the ligaments which bind it to the semilunar. Wittek (according to Deneke) himself fell on his outstretched hand and sustained a fracture of the cuneiform. The condition was not diagnosed at the time, and he suffered considerable disability lasting for more than a year.

Treatment.—Immobilization in plaster-of-Paris for three weeks is followed by no recurrence of the symptoms, and union takes place rapidly.

Illustrative Cases

Case 1.—The patient, a housewife aged 65, fell in the street on to the palm of her hand. On admission to hospital there