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LUNG TUMOURS IN MICE AND MAN

BY

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(WITH SPECIAL PLATE)

Tumours

As the result of more than ten years' experiments (Campbell, 1934-1942b) in which mice were exposed once an hour for six hours on five days of each week for a year to a moderate cloud of dust from various substances, enough data have now been obtained for some general statistical examination. It is possible to compare with some confidence the results elucidated from statistics of human lung cancer (Kennaway and Kennaway, 1936; Turner and Grace, 1938; and others) with results obtained from the above prolonged dusting experiments with mice. Herein some comparison is made between mice and man: (1) as regards agents which increase the incidence of lung tumours; (2) as regards the morphology of the tumours; (3) as regards the time factor or influence of age; and (4) as regards the factors of susceptibility and heredity. Reference is also made to the influence of irritation, both chemical and mechanical.

Full details of the methods of investigation and of the sources and compositions of the various dusts have been given in the previous publications, and will not be repeated here.

some workers with a nickel dust mixture, and Czechoslovak pitchblende miners, while a somewhat high incidence has been observed in those whose occupation exposes them especially to road dust; these latter include paviers, road sweepers, and drivers of horse-drawn and motor vehicles. The inorganic substances, therefore, which appear to be dangerous are radium, arsenic, a "nickel" dust mixture, chromates, iron, and silica. As regards the new carcinogenic agents, the benzpyrene of tar and tarred road dust is more than under suspicion, while this substance is also suspected of causing lung cancer in heavy smokers, being present in small quantity apparently in the tarry matter as the result of combustion of tobacco at high temperatures; some positive results have been obtained in experiments with animals with this tarry matter.

Many of the above substances have been tested on mice, and the significance of the results for various dusts is given in Table I, by means of the statistical ratio of the difference between the percentage incidences of lung tumours in the dusted mice and the control mice to the standard error of the difference (Table I, column 5); the meaning of this ratio is given briefly in column 6 of the same table. It will be observed that the statistical evidence in favour of the particular dust increasing

TABLE I.—Significance of Increase in Incidence of Lung Tumours in Dusted Mice

Ratio (R) Numerical Order	Experiment	Percentage Lung Tumour Incidence		Ratio of Difference between E and C to Standard Error of Difference (R)	Significance of Increase due to Dust
		Dusted Mice (E)	Control Mice (C)		
1	Tarred road dust (1)	74.0	8.0	7.2	Highly significant
2	CO + tarred road dust	47.3	7.5	4.1	
3	Al ₂ O ₃ + SiO ₂ + Fe ₂ O ₃ + CaCO ₃	19.4	0.0	3.6	
4	Fe ₂ O ₃	32.7	9.6	2.9	Definitely significant
5	Czechoslovak dust (2)	20.3	2.1	2.8	
6	Tar-free road dust	44.8	20.0	2.7	
7	Tarred road dust (2)	13.1	1.4	2.6	Some significance, but near borderline
8a	Diluted "nickel" dust	29.8	12.5	2.2	
8b	Czechoslovak dust (1)	11.5	1.7	2.2	
10	Bituminous coal	12.1	1.9	2.1	An increase, but might easily be due to chance
11	SiO ₂ + "nickel" dust	17.4	5.0	1.8	
12a	SiO ₂ + Fe ₂ O ₃	19.4	9.6	1.5	
12b	Carbon, exhaust soot	33.3	20.0	1.5	No increase of any significance
14	Al ₂ O ₃ + SiO ₂ + Fe ₂ O ₃	15.8	9.2	1.1	
15	Steel grindings	13.6	7.7	1.0	
16	Anthracite coal	9.1	7.0	0.4	
17	Coal soot	20.0	20.0	0.0	

Also, full references to literature appeared in these earlier papers, and only key references will now be included. Since lung tumours are very rare in mice younger than 10 months, only older mice are considered. Usually about 80% of the control mice and about 75% of the experimental mice survive for 10 months or longer: as a rule all the mice were allowed to fulfil their allotted span of life. Further, only those experiments in which a visible deposit of dust was apparent in the lungs are at present under review. The experiments with gases and smokes are excluded.

Agents increasing the Incidence of Lung Tumours

The evidence of statistics for human lung cancer indicates that an abnormal liability to this disease has been observed among workers exposed to coal gas and tar, those engaged in the preparation and sale of tobacco, metal grinders, engineers, foundry workers, silica workers, chromate workers,

the incidence of lung tumours is highly significant for a sample of tarred road dust (No. 1), for a sample of a similar dust with carbon monoxide present, and also for a dust mixture containing equal parts of silica, iron oxide, alumina, and calcium carbonate. The increase in incidence of lung tumours in the experimental mice is definitely significant also with a sample of iron oxide, a sample of Czechoslovak pitchblende dust (No. 2) containing a small quantity of radium and arsenic, a sample of tarred road dust from which the tar had been removed by benzene, and a second sample of tarred road dust (No. 2). Experiments in which the increase in incidence is on the borderline of significance include a diluted "nickel" dust mixture, a bituminous coal dust from the South Wales Coal Survey, and another sample of Czechoslovak pitchblende dust (No. 1) containing no arsenic and practically no radium. Experiments in which the increase in incidence might have been due to chance include those with an exhaust soot, those with

steel grindings, and various experiments with silica and iron. Finally, no material difference in incidence was observed in experiments with an anthracite coal dust from the South Wales Coal Survey and a coal soot from a chimney.

When the value of the ratio in column 5 of Table I is 2 it means that such a difference in tumour incidence would arise by chance only once in 20 trials; if the ratio is 2.5 the difference would arise by chance only once in 80 trials, and if 3, only once in 370 trials. For higher values, of course, the risk is very much smaller still. In all the experiments there were about 50 to 60 mice in both the dusted and control groups—that is, 100 to 120 in all. If the same percentage differences between dusted and control mice were to occur with higher numbers of mice they would be of much greater significance. It is thus possible to obtain further evidence that silica and iron increase the incidence of lung tumours by adding all the results together for any of the experiments in which silica and iron were employed. This has been done in Table II, from which it will be seen that of 346 control mice 7.8% possessed lung tumour, while the incidence among 475 mice exposed to various dusts containing either silica or iron, or both, was 20.1%. The value of the above statistical ratio

tumours in susceptible mice, which may explain their presence in the control mice.

Mechanical Irritation

It is possible, of course, that the masses or collections of dust in the lung tissue might cause irritation by mechanical pressure, particularly during the movements of respiration. The harder the dust, or the larger the masses, the greater would be the irritation. Also the clumps of dust might by pressure occlude blood vessels so that a local anoxia might occur, and evidence has been obtained of some influence of anoxia in increasing the incidence of lung tumours in mice (Campbell, 1940a). In addition iron compounds might be freed from any stationary blood or haemoglobin in the occluded capillaries, and a chemical effect of the iron might be thus set up indirectly.

To study more closely any influence of mechanical irritation or pressure it is necessary to have some quantitative method for measuring the experimental dust deposits in the lungs. This is possible with the coloured dusts, and also for colourless dusts if mixed with coloured dusts. From experiments with coal dust and silica it is apparent that the two dusts are ingested by the same cells, so that the extent of the coloured

TABLE II.—*Lung Tumours in Mice in Fe₂O₃ and SiO₂ Experiments*

Experiment	No. of Mice Alive		Animals with Lung Tumours					
	Control	Experiment	Control			Experiment		
			Total	Simple	Malignant	Total	Simple	Malignant
SiO ₂	63	61	5	3	2	13	5	8
Fe ₂ O ₃	—	52	—	—	—	17	3	14
Fe ₂ O ₃ +SiO ₂	52	62	5	3	2	12	5	7
SiO ₂ +methylcholanthrene	66	63	9	5	4	15	11	4
Al ₂ O ₃ +SiO ₂ +Fe ₂ O ₃	65	57	6	3	3	9	6	3
Al ₂ O ₃ +SiO ₂ +Fe ₂ O ₃ +CaCO ₃	60	62	0	0	0	12	5	7
SiO ₂ (93.4%)+“nickel” dust (6.6%)	40	46	2	2	0	8	4	4
SiO ₂ (75–84%)+soda lime (16–25%)	—	54	—	—	—	6	3	3
Totals	346	457	27 (7.8%)	16 (4.6%)	11 (3.2%)	92 (20.1%)	42 (9.2%)	50 (10.9%)

TABLE III.—*Degree of Dusting. Deposit in Lungs and Tracheo-bronchial Lymph Nodes of Mice*

Experiment	Organ	No. of Mice with Deposits								Total No. of Mice with Dust	Average Dust Deposit
		Very Slight, or 12.5%	Slight, or 25%	Slight to Moderate, or 37.5%	Moderate, or 50%	Moderate to Heavy, or 62.5%	Heavy, or 75%	Heavy to Very Heavy, or 87.5%	Very Heavy, or 100%		
Anthracite coal	Lung	0	13	13	15	12	1	1	0	55	45%
Bituminous coal	"	0	0	1	10	9	19	16	11	66	76%
SiO ₂ (93.4%)+“nickel” dust (6.6%)	"	14	8	15	4	0	0	0	0	41	28%
Anthracite coal	Lymph nodes	1	10	6	10	6	5	0	1	39	47%
Bituminous coal	"	1	1	2	7	4	12	10	22	59	79%
SiO ₂ +“nickel” dust	"	7	17	4	3	0	0	0	0	31	26%

from these percentages is 5.2, which indicates that the difference due to the dusting is highly significant. It is likely also that the cause of the increase in incidence of lung tumours in the mice exposed to the road dust with the tar removed (Table I) is also concerned with the iron and silica it contained, as is the increase in the case of the sample of Czechoslovak pitchblende dust (No. 1) which did not contain arsenic or radium.

From the above results it is obvious that so far as many of the causes of the increase in incidence of lung tumours are concerned mice and man show very fair agreement. It is considered that the processes involved are of a prolonged chemical nature—that is, small quantities of the dusts go into solution in the tissues before producing the cancerous effect, possibly the end-result being the same with all the different substances. In most cases the dusting was of a moderate degree or less, so that only moderate deposits or less of dust were present in the lung tissue. Heavier dusting with the apparently inactive dusts might have produced more positive effects. This brings us to the consideration of the mechanical factor due to such deposits. The lungs of the control mice, of course, equally with those of the experimental mice, contain small quantities of dusts from the sawdust of their bedding, from their food, and from their surroundings in general; these dusts may exert some influence in the development of lung

coal-dust deposits covers also that of the colourless silica, as proved by the distribution of the coal and fibrous tissue in the silica nodules in the mouse's tracheo-bronchial lymph nodes. With the aid of the microscope it has been possible to identify four main degrees of deposit, such as slight, moderate, heavy, and very heavy, with four intermediate degrees as indicated in Table III. A very heavy deposit indicates masses of dust which fill up about three-quarters of the lung tissue but do not appear to shorten to any extent the life of the stronger mice. Such a very heavy deposit is arbitrarily termed a 100% deposit. A moderate deposit is half this degree, or a 50% deposit. A very slight deposit indicates scattered specks and particles of the dust. In this way it has been possible to obtain eight degrees of deposit and to estimate by microscopical examination how many mice fall into each of these eight sections. These are all added together to get the total number of mice with dust deposits. Then an average degree of dust deposit for this total is easily calculated from the number and percentage deposit in each of the eight sections. This average is given in the last column of Table III, and by using these averages the degree of deposit in the various experiments may be compared. The same method is employed for the dust deposits in the tracheo-bronchial lymph nodes as shown for some of the dusts in the same table. All the experiments have been dealt with in this way, and the results

are collected together in Table IV, which also records the state of the lymph tissue in the lungs and lymph nodes.

The dusts produced hypertrophy of the lymph tissue in many of the mice. Normally there are very few and scattered collections of lymphocytes near the blood vessels and bronchial tubes in the mouse lung tissue; any definite increase on this

TABLE IV.—Average Dust Deposit and Increase of Lymph Tissue in Lungs and Tracheo-bronchial Lymph Nodes

Lung Dust Deposit Order	Experiment	Lungs		Lymph Nodes	
		Dust Deposit (%)	Lymph Tissue Increase	Dust Deposit (%)	Lymph Tissue Increase
			Dusted Mice % Control Mice %		Dusted Mice % Control Mice %
1	Bituminous coal	76	9.6	79	4.4
2	Tar-free road dust	60	—	66	—
3	Fe ₂ O ₃	59	2.8	45	3.7
4	Carbon, exhaust soot	53	—	47	—
5	Steel grindings	51	6.2	40	2.3
			15.6		
6a	Al ₂ O ₃ +SiO ₂ +Fe ₂ O ₃ +CaCO ₃	46	0.0	30	4.4
6b	CO+tarred road dust	46	—	—	—
8	Anthraccite coal	45	6.1	47	1.8
9a	Tarred road dust (1)	42	—	—	—
9b	Tarred road dust (2)	42	2.0	66	2.8
11	Coal soot	41	—	38	—
12	Dil. "nickel" dust	40	3.1	41	4.3
13a	SiO ₂ +Fe ₂ O ₃	38	2.7	27	2.7
13b	Al ₂ O ₃ +SiO ₂ +Fe ₂ O ₃	38	17.1	25	2.7
15	Czechoslovak dust (2)	35	2.9	62	2.5
16	SiO ₂ + "nickel" dust	28	4.8	26	2.2
17	Czechoslovak dust (1)	21	1.0	31	2.4

is regarded as hypertrophy or reticulosis. Such a hypertrophy occasionally occurs in control mice too, so that it is necessary to divide the percentage of dusted mice with such a condition by the percentage of control mice which also show a hypertrophy. This ratio is given in column 4, Table IV, and indicates the increase in lung lymph tissue due to the dusting.

Normally the tracheo-bronchial lymph nodes are two in number, and if the diameter is more than 2 mm. a hypertrophy is regarded as being present. The increase due to the dusting is shown in the last column of Table IV. This increase in the lymph tissue in the lungs and nodes due to the dusting may not only be an effect of mechanical irritation but also a chemical effect. There does not seem to be any very close agreement between the degree of dust deposit and the increase

indicate in general a mechanical effect. When iron was present many of the "lymph" cells in the lung appeared to be of a sarcomatous type and tended to spread out into the lung tissue; this is apparently a chemical effect (see Plate, Fig. 2).

As regards the influence of the dust deposits upon the incidence of lung tumours, it is perhaps better to consider only the heavier degrees of deposit, such as those termed "moderate to heavy" or heavier, since if mechanical irritation of the dust is a factor in production of lung tumours the heavier dust deposits should be more active than the lighter deposits. Therefore, in Table V the experiments have been arranged in the order of the percentages of the total mice with dust deposits heavier than a moderate degree. The only experiments in which half the mice or more had such heavy deposits were those with bituminous coal, tar-free road dust, and iron oxide. In column 4, Table V, the lung tumour incidences in the dusted mice (E) are given, and a glance shows that in general there is no correspondence with the numerical order of the mice which had heavy dust deposits, so that the heavier degrees of dusting in the main do not control the production of lung tumours. In order to make the comparison accurate it is necessary to consider at the same time also the incidence of lung tumours in the corresponding control groups of mice. This is shown in Table V. From the last column it is evident that all the experiments, when grouped in fours for convenience and clarity, show increases in the incidence of tumours irrespective of the numerical order for the percentages of mice with the heavier dust deposits. It may be concluded, therefore, that in general the increase in incidence of primary lung tumours caused by dusts is a chemical and not a mechanical effect; but it is not possible at present to exclude completely a mechanical factor, since the bituminous coal, tar-free road dust, and iron oxide, with the highest degrees of dust deposit, did produce increases in incidence of lung tumours of some statistical significance. There are cases of lung cancer among coal-miners, but the incidence is low compared with that for certain other industries. In the mouse experiments, too, the bituminous coal does not occupy a very high position (Table I) as a stimulator of lung tumours, although the dust deposit in the lung in this case was the heaviest of all in degree. This bituminous coal and the anthracite coal were obtained through the courtesy of the South Wales Coal Survey Committee, on the suggestion of Dr. P. D'Arcy Hart. The results given herein are merely some preliminary results, the main experiments, undertaken for another purpose, not yet being completed. In the present experiment with anthracite coal the average degree

TABLE V.—Absence of General Dependence of Lung Tumour Incidences in Dusted Mice upon Heavier Degrees of Dust Deposit in Lungs

Degree of Lung Dust Deposit Column 3. Order	Experiment	Total Mice with Deposits classified as "Moderate to Heavy" or Higher (%)	Lung Tumour Incidence				E/C Group
			Dusted Mice (E)		Control Mice (C)		
			%	% for Group	%	% for Group	
1	Bituminous coal	83	12.1	25.8	1.9	9.8	2.6
2	Tar-free road dust	60	44.8		20.0		
3	Fe ₂ O ₃	54	32.7		9.6		
4	Steel grindings	40	13.6		7.7		
5	Carbon, exhaust soot	35	33.3	18.7	20.0	7.1	2.6
6	Anthracite coal	25	9.1		7.0		
7	Al ₂ O ₃ +SiO ₂ +Fe ₂ O ₃ +CaCO ₃	18	19.4		0.0		
8	Tarred road dust (2)	16	13.1		1.4		
9	Coal soot	11	20.0	40.4	20.0	9.4	4.3
10	CO + tarred road dust	10	47.3		7.5		
11	Czechoslovak dust (2)	8	20.3		2.1		
12	Tarred road dust (1)	7	74.0		8.0		
13a	SiO ₂ +Fe ₂ O ₃	2	19.4	18.8	9.6	7.6	2.5
13b	Al ₂ O ₃ +SiO ₂ +Fe ₂ O ₃	2	15.8		9.2		
13c	Dil. "nickel" dust	2	29.8		12.5		
16a	SiO ₂ + "nickel" dust	0	17.4		5.0		
16b	Czechoslovak dust (1)	0	11.5		1.7		

in lymph tissue. There are high increases of lymph tissue in the lung with the highest degree of dust deposit—that is, with the bituminous dust, and also with the dust mixtures containing alumina, which is very hard (Nos. 6a and 13b, Table IV). The hard steel grindings also produced a high increase in lymph tissue in the lungs (No. 5), as did the hard anthracite coal (No. 8). It is obvious that all the dusts increase the lymph tissue in the lungs and lymph nodes, which might

of dust deposit in the lung was less than moderate (Table IV). In the unfinished experiments heavier deposits are expected.

Influence of Age and Sex

The large majority of deaths from human lung cancer occur after the age of 55—that is, in the closing years of life. In mice also, lung tumours are rare until the last quarter of their average existence. These facts indicate the importance of the

time factor and point towards some very prolonged action. This is why the prolonged dusting experiments with mice have been persevered with. It is possible by means of intravenous injection of very small quantities of some new carcinogenic agents to produce lung tumours rapidly in certain strains of mice (Andervont and Shimkin, 1940). It is doubtful whether with such rapid action these results can be applied to the usual cases, in which such prolonged action seems necessary, unless it be assumed that under normal conditions inhibitory agents may also be present, as seems to be the case in some strains of mice whose lungs are very resistant even to intravenous injection of powerful carcinogens (Heston, 1942).

Although in mice and man the incidence of lung tumours is highest in the closing years of life, it might be argued that the resemblance is superficial, because a mouse lives only two or three years. In reply it may be stated that the rate of respiration is higher in the mouse than in man, and all metabolic processes seem speeded up in these small animals. At any rate, in both mice and man a relatively prolonged action of the dust seems necessary for the production of lung tumours under ordinary conditions.

In human lung cancer, males appear to be affected much more often than females, but some observers find that for simple adenoma the reverse is the case. With mice, on the whole, sex does not appear to play any great part, but in the case of the experiments both male and female mice were exposed equally to the adverse conditions. In man environmental conditions are usually different for the two sexes for a great part of the day. The entry of women into industry during the war may in time change the distribution of human lung cancer.

Influence of Heredity and Susceptibility

The milk factor recently discovered by Bittner to be so important for the development of mammary tumours in mice has apparently no influence on the incidence of lung tumours; but it is evident that by inbreeding with brother-to-sister matings it is possible to produce strains of mice either very susceptible or very resistant to development of lung tumours (Strong, 1936; Bittner, 1939; Murray, 1934; Little *et al.*, 1939; Furth *et al.*, 1933, 1941). In this respect heredity is important, and in man there is a suspicion that some such inbreeding has had an influence in the production of the high incidence of lung cancer in the Czechoslovak pitchblende miners, although the radium, arsenic, or some other inorganic substance may act as the trigger in the mechanism of its development. These substances, however, do not appear to be so active in similar miners in other places, so that heredity due to a certain amount of inbreeding in the case of the Czechoslovak miners may explain the difference. Even with this mechanism the cancers often appear only long after the miners have left the mines, so that the time factor is of great importance here too. In this Czechoslovak region there are also cases among men who have never been in the mines and have worked outside them altogether, which seems to point

to an influence of heredity or some factor present in the outside dust as well as in the mine dust.

In the above mechanism of heredity genes presumably would be active. Nucleoprotein, it is said, forms part of the constitution of genes, and it appears that the same holds good for at least some viruses (Stanley and Knight, 1941). It is tempting to suggest that some link or chain in nucleoprotein may provide the bridge between the heredity theory and the so-called virus theory held by some observers for cancer in general. So far there is no evidence that a virus is concerned in lung tumour development, unless a virus is similar to a gene.

As a rule human populations, compared with closely inbred mice, are of very mixed strains, so that in man any influence of heredity must be much thinned out and scattered about, as it is in mixed strains of mice such as those used in the present experiments (Campbell, 1942b). Owing to this thinning-out of susceptibility in mixed strains, relatively large numbers of mice are required for each experiment. Human statistics in such a condition can hardly help in the solution of the problem unless it is realized that, as in the mouse, the mechanisms of development may be manifold and complex. Thus a very susceptible individual living in a moderately dusty atmosphere might be affected while an insensitive individual in a similar but very much dustier atmosphere might escape. It is this problem of susceptibility that at present interferes with the complete elucidation of the mechanism of lung tumour development. Although it is possible to name some factors which increase the incidence of lung tumours in mice and man, the ultimate *fons et origo* of the tumour itself remains obscure. Nevertheless it is obvious that dusts suspected or proved to be dangerous should be reduced as much as possible in industry and elsewhere.

LEGENDS FOR SPECIAL PLATE

Magnification in all cases $\times 200$

FIG. 1A.—White mouse, male, aged about 22 months; exposed to bituminous coal dust for 1 year. Part of edge of lung cancer with oatlike cells (early stage) advancing on walls of adjacent alveoli. Weigert, van Gieson.

FIG. 1B.—Metastasis, in tracheo-bronchial lymph nodes, of large oatlike cells from a similar part of lung tumour; another part of which is shown in Fig. 1A. Weigert, van Gieson.

FIG. 2.—Fawn mouse, female, aged about 27 months; exposed to dust mixture $Al_2O_3 + SiO_2 + Fe_2O_3$ for 1 year. Small oatlike and sarcomatous cells (mostly transverse section) in part of adenocarcinoma. Haematoxylin, eosin.

FIG. 3.—White mouse, female, aged about 21 months; exposed for 1 year to a diluted Czechoslovak pitchblende dust (2), containing some inorganic substances, including radium, arsenic, silica, and iron. Lung cancer cells with formation also of fibrous tissue. Haematoxylin, eosin.

FIG. 4.—White mouse, male, aged about 29 months; exposed for 1 year to a diluted Czechoslovak pitchblende dust (1) without arsenic and radium. Transitional area from papillo-adenocarcinoma to oatlike and spindle cells. Haematoxylin, eosin.

FIG. 5.—Fawn and white mouse, female, aged about 21 months; exposed for 1 year to road dust minus tar. Part of lung cancer with various types and conditions of cancer cells. Haematoxylin, eosin.

FIG. 6A.—White mouse, female, aged about 21 months; exposed for 1 year to Fe_2O_3 dust. Primary lung cancer, papillomatous nature. Haematoxylin, eosin.

FIG. 6B.—Metastasis, in tracheo-bronchial lymph nodes, of glandlike cells from lung cancer in Fig. 6A. Haematoxylin, eosin.

FIG. 7A.—White mouse, female, aged about 27 months; exposed to steel-grindings dust for 1 year. Lung cancer. Haematoxylin, eosin.

FIG. 7B.—Metastasis near oesophageal wall (note muscle coat) from lung cancer in Fig. 7A. Haematoxylin, eosin.

FIG. 8A.—Chocolate mouse, male, aged about 25 months; exposed to a mixture of SiO_2 + a nickel dust mixture for 1 year. Lung cancer with spindle and other cells. Weigert, van Gieson.

FIG. 8B.—Metastasis in tracheo-bronchial lymph node of oatlike cells from lung cancer in Fig. 8A. Some remains of lymph cells are seen in top right-hand corner. Weigert, van Gieson.

Morphology of Lung Tumours

Many types of tumour cells are represented in the mouse lung tumours obtained in these experiments. There are simple adenomas, and very malignant tumours with extensions into other organs. Eighteen cases of such extensions into other organs have now been obtained among the experimental mice and only two such cases among the control groups. The most common extension is into the tracheo-bronchial lymph nodes, but extensions have been observed also in the heart, chest wall, and kidney. The tumours seem to arise often in collapsed areas of the lung, usually near the pleura; the cells become more or less cubical, and it is not possible to decide whether these cells arise from cells of the alveoli or as extensions from the terminal bronchioles. Many types of malignant cells may be found in one and the same mouse tumour, with transitions from the usual cells seen in adenocarcinoma to spindle-like cells or the larger and smaller oat cells, or to sarcoma-like cells. Some illustrations of these tumours and their metastases have been published (Campbell, 1937a), and others not yet represented are shown in the accompanying twelve photographs

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(For legends see text)

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taken by Mr. F. V. Welch of this institute (Plate, Figs. 1a to 8b). At one time mouse tumours were all considered to be simple and non-metastatic because evidently they were observed only in younger mice, the mice being killed early. This idea can no longer be held, and there seem to be really no fundamental differences from human lung tumours. Benign adenomas occur in man similar to some seen in mice. Human lung cancer cells are generally classified as squamous, columnar, spheroidal, polygonal, round, and oat: representatives of all these have been seen in mouse cancers, although there may be some minor differences. In mice, although some cases of epidermoid cancer occur (Wells *et al.*, 1941), the squamous cells are seen in their lungs usually only as metastases from skin cancer due to painting the mouse's skin with tar. In man, metastases are seen more often than in the mouse, but this may be due to differences in the vascular beds or to the erect position of the human body. Also, metastases in the brain are common in man but, so far as is known, have not yet been reported there for the mouse, although one has been reported in the skull (Wells *et al.*, 1941). In addition human lung cancers are usually described as bronchiogenic, while only a few of the mouse cancers seem so closely connected with the larger bronchi; but it seems impossible to exclude completely some connexion with terminal bronchioles. Often the mouse lung cancers are described as alveolar cancers, while only 5% of human lung cancers are thus designated (Neubuerger and Geever, 1942). Such differences may be due merely to the different lay-out of the lungs in mice and man. It may be concluded that there are no sound reasons why the results obtained with the mouse experiments may not be applied to human beings. Certainly the dust experiments often seem to produce malignant tumours similar to those seen in man.

Summary

There is a similarity between human lung cancers and mouse lung cancers as regards: (1) agents which increase the incidence of these tumours; (2) the time or age factor; (3) some aspects of the factor of susceptibility; (4) morphology of the tumours.

Although the main effect of certain dusts in development of lung cancer appears to be of a prolonged chemical nature, it is not possible at the moment to exclude entirely some effect of prolonged mechanical irritation by the harder or larger collections of dust. A method for comparison of the degree of dust deposit in the various experiments is given for the first time.

The increase in incidence of lung tumours in mice by certain dusts—tarred road dust with and without the tar, Czechoslovak pitchblende dust, iron oxide, silica, a "nickel" dust mixture—is statistically significant, although in most cases the average deposits of dust in the lungs are of moderate degree only or less. Care should be taken to reduce exposure to these dusts.

Dusts produce a hypertrophy of lymph tissue in the lungs and in the tracheo-bronchial lymph nodes.

Some further illustrations of mouse lung cancers and their metastases are given.

There is no fundamental reason why the results obtained in mouse experiments with dusts should not be applied to man.

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REFERENCES

- Andervont, H. B., and Shimkin, M. B. (1940). *J. nat. Cancer Inst.*, **1**, 225.
 Bittner, J. J. (1939). *Publ. Hlth. Rep. Wash.*, **54**, 380.
 Campbell, J. Argyll (1934). *Brit. J. exp. Path.*, **15**, 287.
 — (1936). *Ibid.*, **17**, 146.
 — (1937a). *Ibid.*, **18**, 215.
 — (1937b). *J. industr. Hyg.*, **19**, 449.
 — (1939). *Brit. J. exp. Path.*, **20**, 122.
 — (1940a). *British Medical Journal*, **1**, 336.
 — (1940b). *Ibid.*, **2**, 275.
 — (1942a). *Ibid.*, **1**, 217.
 — (1942b). *Brit. J. exp. Path.*, **23**, 191.
 Furth, J., Seibold, H. R., and Rathbone, R. R. (1933). *Amer. J. Cancer*, **19**, 521.
 — and Barnes, W. A. (1941). *Cancer Res.*, **1**, 17.
 Heston, W. E. (1942). *J. nat. Cancer Inst.*, **3**, 69, 79.
 Kennaway, N. M., and Kennaway, E. L. (1936). *J. Hyg., Camb.*, **36**, 236.
 Little, C. C., Murray, W. S., and Cloudman, A. M. (1939). *Amer. J. Cancer*, **36**, 431.
 Murray, W. S. (1934). *Ibid.*, **20**, 573.
 Neubuerger, K. T., and Geever, E. F. (1942). *Arch. Pathol.*, **33**, 551.
 Stanley, W. M., and Knight, C. A. (1941). *Cold Spring Harbor Symposia on Quantitative Biol.*, **9**, 255.
 Strong, L. C. (1936). *J. Hered.*, **27**, 21.
 Turner, H. M., and Grace, H. G. (1938). *J. Hyg., Camb.*, **38**, 90.
 Wells, H. G., Slye, M., and Holmes, H. F. (1941). *Cancer Res.*, **1**, 259.

THE WAR NEUROSES: THEIR NATURE AND SIGNIFICANCE

BY

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The following conclusions which I have reached regarding the nature of the so-called "war neuroses" are based upon my experience of psychopathological conditions among military personnel during the present war, and more particularly in a special hospital which until recently formed part of the Emergency Medical Service.

The Traumatic Factor

The term "war neuroses" covers a great variety of clinical conditions; and there is now fairly general agreement among psychiatrists that, so far as symptomatology is concerned, the war neuroses possess no distinctive features differentiating them sharply from the various psychoneurotic and psychotic states which prevail in time of peace. Some psychiatrists have accordingly suggested that it would be more accurate to speak of "the neuroses in wartime" than to speak of "the war neuroses." On the other hand, there are psychiatrists who maintain that where cases among military personnel are concerned a distinction must be drawn between (1) a group of psychopathological states which appear to be precipitated by active warfare and (2) familiar psychopathological states which chance to occur during the course of military service but which might equally well have occurred in civilian life. This attempted distinction appears to be based on the observation that in an appreciable proportion of military cases a psychopathological state is found to have supervened upon some traumatic experience associated with warfare (e.g., a near shell-burst or bomb explosion). In contrast to this observation it is to be noted that "traumatic neuroses" are by no means unknown in time of peace; and here it must be kept in mind that, if such neuroses are less common in peacetime than in wartime, so also are violent traumatic experiences themselves. Actually it is not uncommon to find that a soldier suffering from a traumatic neurosis acquired in war has a previous history of a traumatic neurosis acquired in civilian life. In an appreciable percentage of military cases, too, the trauma upon which a "war neurosis" supervenes is found to be one (e.g., a motor accident) which is only incidentally associated with conditions of war. It is impossible, however, to dismiss the question of the part played by traumatic experiences in the precipitation of war neuroses without pausing to consider what constitutes a traumatic experience.

It is all too often assumed that a traumatic experience is one which produces a psychopathological state *de novo*. Yet, when investigation is sufficiently painstaking, it is rare to find a case in which evidence of pre-existing psychopathological characteristics cannot be detected in the previous history. It is reasonable to conclude, accordingly, that a traumatic experience is one which serves to precipitate a psychopathological reaction through the activation of pre-existing but hitherto latent psychopathological factors. The correctness of this conclusion is confirmed by the fact that in certain cases it is possible to detect a very high degree of specificity in the traumatic experience.

Admittedly in many cases the specificity of the traumatic experience is by no means easy to establish. Nevertheless this in itself may not be without significance once the principle of specificity has been recognized. Significance may also be attached to the fact that in many cases it is far from obvious why a situation precipitating a psychopathological state should possess any traumatic quality at all; for many experiences which prove to be traumatic appear comparatively trivial in themselves. Investigation reveals a remarkable range of traumatic experiences, as may be illustrated by the following examples chosen more or less at random from cases that have come under my notice: being blown up by a bomb, being trapped in the cabin of a torpedoed ship, seeing civilian refugees massacred, having to throttle a German settler in self-defence, being let down by an officer in a tight corner, being accused of homosexuality by another soldier, being refused compassionate leave to go home for a wife's confine-

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