STUDIES ON THE RELATION BETWEEN TUMOR SUSCEPTIBILITY AND HEREDITY.

III. Spontaneous Tumors of the Lung in Mice.

By CLARA J. LYNCH, Ph.D.

(From the Laboratories of The Rockefeller Institute for Medical Research.)

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In discussing cancer from the standpoint of heredity the present tendency is to regard susceptibility to the development of tumors of each tissue or of each organ as if inherited separately. In a previous communication[1] from this laboratory evidence was presented in favor of the view that susceptibility to tumors of the mammary gland in mice is influenced by the laws of heredity and that it apparently behaves as a dominant though variable character. The present paper is concerned with the inheritance of susceptibility to tumors of the lung in mice.

Lung tumors as well as mammary gland tumors are not uncommon in mice. They have been reported by Livingood,[2] Tyzzer,[3] Jobling,[4] Haaland,[5] Slye, Holmes, and Wells,[6] and others. Tyzzer[3] states that growths appear to be more frequent in the lung than in any other organ. In 70 tumor mice which he examined, 83 neoplasms were found. 74 per cent of all the individuals had pulmonary tumors and 62 per cent of all the tumors were in the lung. A stock of mice which was under observation for 2 years yielded 12 mice (9 females and 3 males) with lung tumor from 500 autopsies. Haaland[5] found pulmonary tumors next in frequency to mammary tumors. Complete statistics are not given. In the

[1] Lynch, C. J., *J. Exp. Med.*, 1924, xxxix, 481.

[2] Livingood, L. E., *Bull. Johns Hopkins Hosp.*, 1896, vii, 177.

[3] Tyzzer, E. E., *J. Med. Research*, 1907, xvii, 155, 199; 1909, xxi, 479.

[4] Jobling, J. W., Spontaneous tumors of the mouse, Monograph of The Rockefeller Institute for Medical Research, No. 1, New York, 1910, 81.

[5] Haaland, M., *Ann. Inst. Pasteur*, 1905, xix, 165; *4th Scient. Rep. Imperial Cancer Research Fund*, London, 1911, 1.

[6] Slye, M., Holmes, H. F., and Wells, H. G., *J. Med. Research*, 1914, xxx, 417.

Slye stock[6] also lung tumors were found to be second to mammary gland tumors in frequency. 160 mice with pulmonary nodules were observed in 6000 autopsies (2.7 per cent) and one-third of all tumors found arose in the lung. A large number of cases have been discovered in this laboratory. As a result of the practice of making autopsies on all mice data have accumulated regarding the occurrence of pulmonary tumors in mixed populations and also in certain strains of mice that have been closely inbred. Since in many of the groups under observation a large number of the individuals of the more recent generations are not yet dead this preliminary report covers results from only a few of the earlier crosses in which the data are practically complete.

Several investigators have already published contributions to the subject of the hereditary aspect of tumors of the lung. Tyzzer[3] observed the tumor incidence in several inbred families of mice. In the largest group (Family A) there were 98 descendants belonging to several generations derived from an original mating of a mouse which never developed tumor with a female which was found to have a cystadenoma of the lung. Of 62 which died after reaching full maturity 20 developed one or more tumors, 17 being pulmonary tumors. If the mice of this family are classified according to whether they are the offspring of parents without tumors or of parents one of which developed a tumor, it is found that in the first group, 9 mice in a total of 67 (13 per cent) were tumor mice while in the second group 11 out of 28 (39 per cent) developed tumors. If only those individuals which lived more than 6 months are included in the estimates, among the 40 offspring born of tumor-free parents 23 per cent developed tumors while among 24 mice with one tumor parent 50 per cent developed tumors. Tyzzer concluded that although the numbers dealt with were small, the data tended to indicate that there is a stronger tendency to the development of tumors in the offspring of parents with tumors than in the offspring of parents which are free from tumors.

Slye, Holmes, and Wells[6] have published data from 6000 autopsies. In their stocks lung tumors do not ordinarily appear in mice younger than 12 months and about one-third of the individuals died under that age. 155 mice with lung tumors were investigated from the standpoint of heredity. Of these 146 were found to have a tumor ancestry but 9 of the cases of lung tumor appeared in mice without tumor ancestry and these 9 tumors were all benign. Since one-third of the mice autopsied were from non-cancerous strains, if inheritance played no part, there should have been 50 cases instead of 9 in these strains. The authors cited believe that in mice without cancer ancestry inflammatory reactions in the lungs seldom become neoplastic in character; that if excessive proliferation occurs in such individuals it does not exceed that of a slight papillary growth; and that heredity modifies the nature or degree of reaction to injury.

In the present paper no attempt has been made to classify the tumors according to the degree of malignancy shown by them. The histological aspect of tumors of the lung in mice was first described by

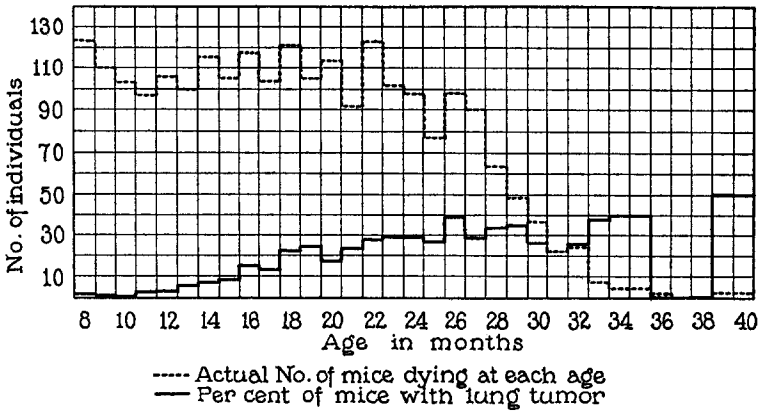
Livingood[2] and it has been the subject of so many communications since then that a detailed account is unnecessary here. A considerable variation exists in their behavior. Many show no evidences of malignancy while others appear to be actively growing, infiltrating the surrounding tissues in the lung or the mediastinum. They are often multiple. The neoplastic epithelium frequently resembles the bronchial epithelium, although examples in which it is like thickened alveolar epithelium are also found. We have encountered no tumors in this material like the epidermoid carcinoma of the lung described by Tyzzer. It is sometimes difficult to distinguish between neoplastic and inflammatory hyperplasia and several cases in our material have been classed as doubtful. Under this heading are also included a few mice in which pulmonary nodules were found at autopsy but in which postmortem changes made a histological verification impossible. The growths vary greatly in size. Sometimes they are so small as to escape detection at autopsy and are found only by chance in sections. Serial sections of the lung were not made so that in general only those nodules large enough to be visible to the naked eye are included in the data. The mice were allowed to live under conditions as nearly natural as a laboratory permits and the tumors under discussion were "spontaneous." Besides the lung tumors there were found in the material 7 sarcomas, 3 of which were in animals which also had lung tumors, and 8 epitheliomas of the jaw, 3 of which coexisted with tumors of the lung. One mouse with a lung tumor had a carcinoma in the ovary and 2 mice had carcinomas of the stomach. There were also a large number of tumors of the mammary gland. In fact the stocks of mice studied served as a source of supply for mammary neoplasms. The majority of the mice developing them were used in other experiments or disposed of outside this laboratory and so few of the records dealing with such animals, valid for the condition of the lung, are available that it was decided to omit them in the interest of a more uniform basis for conclusions. There are very few data from other laboratories regarding the percentage of lung tumors which occurred in the total number of mice with mammary gland tumors and also in the total number of mice free from such growths. Jobling, in a small series of mice with mammary neoplasms, found that pulmonary growths occurred in about one-third of the individuals while none appeared in several

thousand mice free from tumors of the mammary gland. The ages of these mice are not given. The few facts we have accumulated which bear on this point would tend to indicate that in our stock lung tumors coexist with mammary gland tumors in about the same per cent with which they occur in individuals free from mammary gland tumors. In an inbred strain in which the rate of incidence of lung tumors was 6.7 per cent among females free from mammary gland tumors there were 23 animals developing tumors of the mammary gland, in which the lungs also were examined. Only one of these had developed a primary pulmonary tumor.

The data which have been accumulated furnish information upon the rates of incidence of spontaneous tumors of the lung in mice (1) in relation to age and sex, (2) in two inbred strains of mice, (3) in the offspring from parents with and without pulmonary tumors, and (4) in the offspring from crosses between strains that have a high and a low rate, respectively, in regard to tumors in the lung.

1. Rates of Incidence of Spontaneous Tumors of the Lung in Relation to Age and Sex.—It has been noted that tumor rates vary markedly with the age of the individuals concerned although it is not clear whether this is a direct effect of the "age" of the tissues or indirectly due to the fact that a long life offers more opportunities for exposure to the various forms of chronic irritation which induce neoplastic disease. The earliest age at which a lung tumor has been found in these strains is 8 months and the greatest age is 40 months. They occur most frequently in mice of about 24 months or older. In one group of 1500 autopsies upon mice from the general stock the maximum rate of lung tumor incidence was 45 per cent at 26 months of age. In another group of about equal size the maximum rate of 38 per cent was reached at 29 months. The two groups taken together give a lung tumor incidence of about 17 per cent in 2300 mice which were over 7 months of age and 11 per cent in 3500 mice of all ages. These figures do not include mice with mammary tumors. We can follow the monthly fluctuation of the tumor rates in these two groups combined, in Text-fig. 1. This shows the actual numbers of mice dying at each age and the percentage of tumor mice occurring among them. At the younger ages (8 to 12 months) the tumor rate lies at the low level of 1 to 3 per cent. Beginning with the 13th month there is a gradual

increase in the rate and from the 22nd through the 29th month it is maintained at a level of about 30 per cent. At 26 months a rate of 39 per cent is shown and at 29 months it is almost as high. After the 29th month the rate declines slightly. The large percentages shown at 33 months and older are based on less than 10 mice in each group. If these individuals are classed together the incidence for the total number is 38 per cent, about the same rate as that given at 26 months. It is interesting to note that 2 mice died at 39 months and 2 at 40 months, and in each case 1 of the individuals was free from growths in the lung.



TEXT-FIG. 1.

Sex is probably not of importance in determining the occurrence of primary tumors of the lung. Slye, Holmes, and Wells report that 57.4 per cent of the lung tumors in their stock were found in females and 42.6 per cent in males. The reverse condition was found to exist in our stocks, as the higher percentage was shown by the males. Reference to Text-fig. 6 which gives ratios for the males and females of mixed ancestry shows that the percentage of lung tumors at the different age periods was consistently higher for the males than for the females. For the males of all ages combined it was 50 per cent compared with 26 per cent for the females. In Text-fig. 3 we see that also in the inbred Strain 1194 the males have a higher lung tumor rate (13 per cent) than do the females (4 per cent) and in the inbred Bagg strain 35 per

cent of the females had lung tumors whereas 45 per cent of the males developed them. In the larger group of 2300 individuals from a variety of sources the rate of incidence was 16 per cent for the females and somewhat greater, 22 per cent, for the males. Whatever factors may explain the high per cent of tumors among the males in certain instances in our stock (it was frequently 2 or more times as high as among the females) sex certainly is not nearly so potent a factor in determining the occurrence of tumors in the lung as it is in affecting tumors of the mammary gland, which are restricted almost entirely to the female sex, having been rarely reported in males.

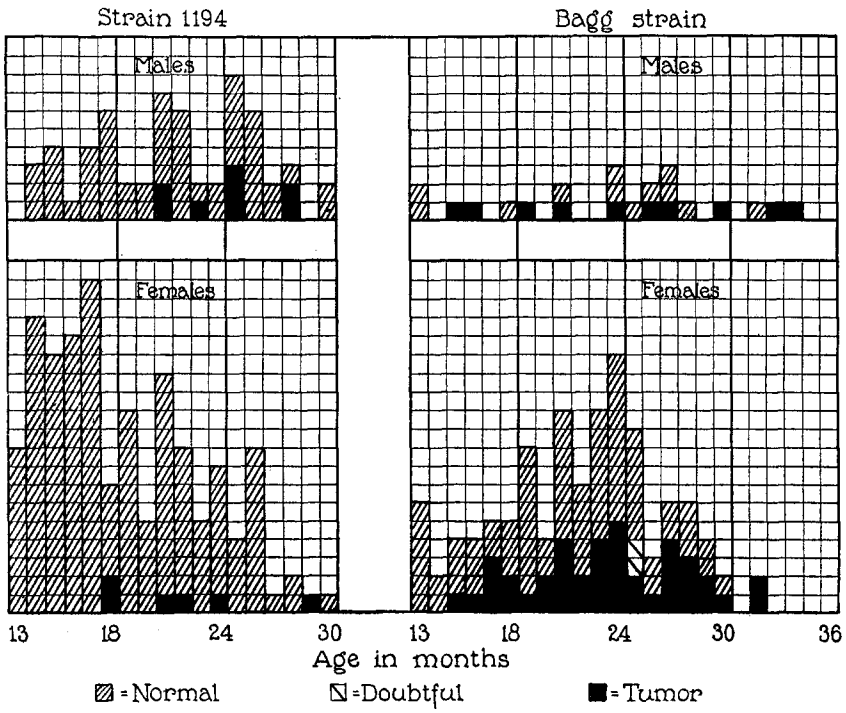
2. Rates of Incidence of Spontaneous Tumors of the Lung in Two Inbred Strains of Mice.—Different strains of mice show differing rates of incidence of tumors of the lung but two inbred strains have been discovered which present a marked contrast to each other.

Strain 1194 is one of the Lathrop stocks and was derived originally from a cross between a male of one tumor strain and 2 females from another strain. Their descendants were inbred probably rather closely for four generations before they were acquired by this laboratory. One pair of mice in the fifth generation gave rise to the present strain and their offspring have been bred brother by sister (or rarely, cousin by cousin) since that time. These data include individuals from the sixth to the fifteenth generation. Most of the mice are black agouti like the wild house mouse though a few are pink-eyed or brown agouti. The stock has a low rate of incidence for tumors of the lung but a high rate for tumors of the mammary gland. Growths may appear in the mammary gland when the mouse is but 5 months of age but in this strain they usually appear at about 12 months. 65 per cent of the females that have been bred and live to be 6 months old and 20 per cent of those that have not been bred have mammary gland tumors. Tumors of the lung are noted only at autopsy. Though they may appear when the mouse is but 8 months old in the general stock, in this strain the youngest age at which a lung tumor was found was 18 months. In all, there were but 14 animals with lung tumor out of a total of 208 mice that lived to be a year old—a rate of 6.7 per cent.

For comparison with Strain 1194 we may cite the Bagg strain of albinos. This stock in contrast with Strain 1194 has a high incidence of lung tumors and a lower incidence of mammary gland tumors. It is impossible to say whether or not any significance attaches to the fact that each strain gives a high and a low tumor rate but in the opposite type of tumor. The data cover a group of 30 or 40 mice from a stock which had been rather closely inbred for several years previous to their acquisition by us and also two generations from a half dozen pairs which were inbred brother by sister. Among females which have been bred,

mammary gland tumors occur in about 27 per cent and in 4 per cent of females over 6 months that have not been bred; while in a total of 135 individuals over 12 months tumors of the lung are found in 37.04 per cent.

Since age and sex in regard to tumor production are of interest, the distribution of the individuals in the two strains is presented graphically in Text-fig. 2 and a summary of the ratios arranged in age periods of 6 months each is given in Text-fig. 3. The mortality of females under



TEXT-FIG. 2.

18 months of age was greater in Strain 1194 than in the Bagg strain and tumors did not appear until the 18th month in the first strain as compared with the 15th month in the Bagg albinos. Although some of the totals are small, in each of the age periods for both males and females the ratio of tumor to non-tumor individuals is higher in the Bagg strain than it is in Strain 1194. Among the Bagg males of all ages over 12 months there were 10 mice with lung tumors and 12 non-

tumor mice (45 per cent of lung tumors), whereas in Strain 1194 there were 8 males with tumors and 52 non-tumor males (13 per cent). Among the females, the ratio in the Bagg strain was 40 tumor mice to 73 non-tumor mice (35 per cent) and in Strain 1194 there were 6 tumor mice to 142 non-tumor mice (4 per cent). Combining individuals of both sexes and all ages the rate of incidence of tumors of the lung in the Bagg strain was 37.04 per cent ± 2.80 in a total of 135 mice and in Strain 1194 it was only 6.73 per cent ± 1.17 in a total of 208 mice. The difference between the tumor rates of the two strains is 30.31 ± 3.04. Since the difference is almost 10 times the probable error the

Females

Strain	Age, 13-18 mos.		19-24 mos.		25-36 mos.		Total		
	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor	Per cent
Bagg strain	19	7	38	18	16	15	73	40	35
Strain 1194	77	2	48	3	17	1	142	6	4

Males

Strain	Age, 13-18 mos.		19-24 mos.		25-36 mos.		Total		
	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor	Per cent
Bagg strain	3	2	3	3	6	5	12	10	45
Strain 1194	18	0	18	3	16	5	52	8	13

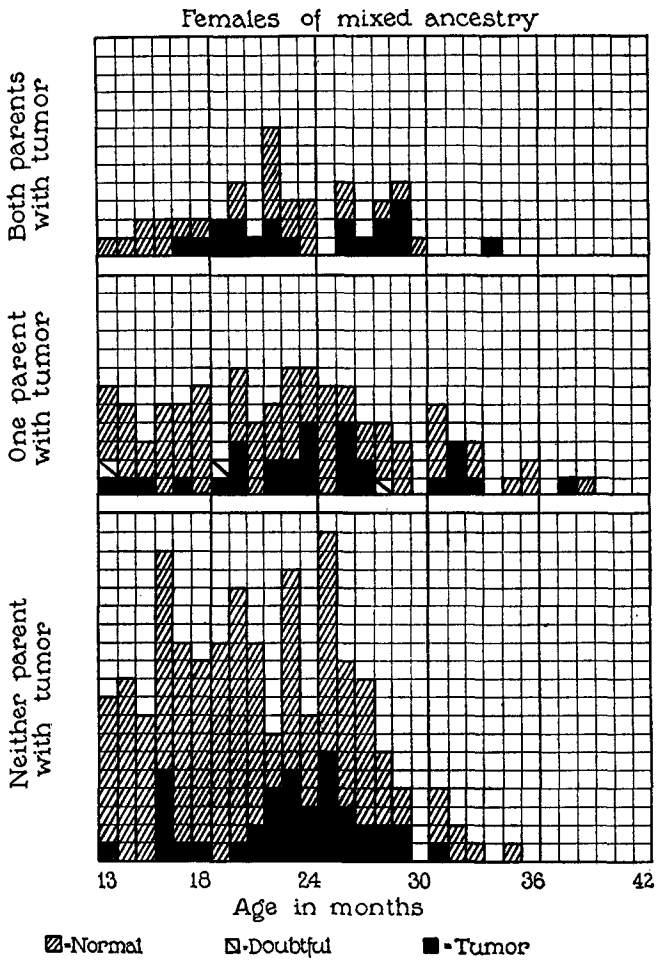
TEXT-FIG. 3.

chances are enormously against its being due to fluctuations in sampling. We may conclude that it is undoubtedly significant.[7]

3. Comparison of Rates of Incidence among the Offspring of Parents Which Have and of Parents Which Have Not Developed Primary Tumors of the Lung.—Records are available of a very mixed population derived from crosses between mice from a variety of sources. The offspring from these matings may be grouped in three classes: mice (1) from parents in which no lung tumors were found, (2) from parents one of which developed a lung tumor, and (3) from parents both of which

[7] The probable error of the percentages was calculated by the method given by Haldane (Haldane, J. B. S., *J. Genetics*, 1919, viii, 291).

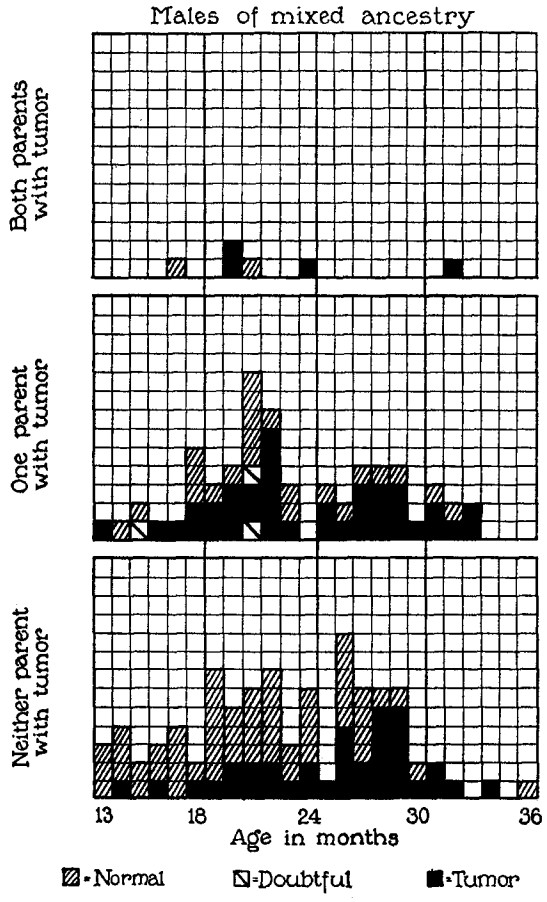
developed lung tumors. In certain cases the autopsy record of one of the parents was not available for reasons already stated. The offspring of such a parent were included in the data, the parent being classed as a non-tumor mouse. This procedure is justified because the



TEXT-FIG. 4.

data include also mice from parents which died younger than the earliest age at which tumors have ever been seen and because at best the classification is inexact. Probably many mice never produce tumors

although they have an inherited capacity to do so. Such individuals must be classed as non-tumor mice whereas genetically they are tumor mice. Class 1, above, which comprises mice from non-tumor parents probably includes individuals which should go in Class 2 or



TEXT-FIG. 5.

3, and Class 2 probably includes mice of which both parents were genetically speaking tumor mice and should have been put in Class 3. The males and females are grouped separately and the age distribution of the three classes for each sex is shown in Text-figs. 4 and 5. The distribution of deaths covers about the same range for the three

Females of mixed ancestry

Type of mating	Age, 13-18 mos.			19-24 mos.			25-30 mos.			31-36 mos.			37-40 mos.			Total		
	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors
0×0	59	8	12	55	15	21	34	15	31	7	1	13	0	0	0	155	39	20
T×0	25	4	14	19	12	39	16	6	27	9	5	36	1	1	50	70	28	29
T×T	8	2	20	12	8	40	5	8	62	0	1	100	0	0	0	25	19	43

Males of mixed ancestry

Type of mating	Age, 13-18 mos.			19-24 mos.			25-30 mos.			31-36 mos.			37-40 mos.			Total		
	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors	No tumor	Tumor	Per cent tumors
0×0	15	3	17	24	10	29	12	18	60	1	4	80	0	0	0	52	35	40
T×0	5	5	50	10	14	58	5	13	72	2	5	71	0	0	0	22	37	63
T×T	1	0	0	1	3	75	0	0	0	0	1	100	0	0	0	2	4	67

0×0 = neither parent with tumor
T×0 = one parent with tumor
T×T = both parents with tumor

TEXT-FIG. 6.

classes when their respective age periods are compared. The occurrence of the doubtful cases is indicated on the graphs but they are omitted from the summary of the ratios which is given in Text-fig. 6.

The data for both sexes show that the rate of incidence of tumors of the lung is higher among the offspring when the parents are known to have developed lung tumors than when the parents were tumor-free.

Among the females of all ages in the first class (from tumor-free parents) there were 155 non-tumor mice to 39 tumor mice, or 20 per cent; in the second class (in which one of the parents developed a lung tumor) there were 70 non-tumor to 28 tumor mice, or 29 per cent; in the third class (in which both parents had tumors) the percentage of tumors increased still more as there were 25 non-tumor and 19 tumor mice, or 43 per cent. Among the males, in the first class there were 52 non-tumor and 35 tumor mice, or 40 per cent and in the second class, 22 non-tumor mice to 37 with tumors, or 63 per cent. There were but 6 individuals in the third class but 4 of them developed tumors. Examining the ratios for the different age periods we find evidence of the same increase in tumor rate in the groups which have a tumor ancestry over groups with a non-tumor parentage. Among the females between 12 and 18 months of age the rate increases slightly from 12 per cent in the first class to 14 per cent in the second. In the third class there are but 10 mice but 2 of them (20 per cent) had lung tumors. Females between 19 and 24 months in the first class had a tumor rate of 21 per cent; in the second class 39 per cent and in the third class 40 per cent. In the age period between 25 and 30 months is found one of the two instances in which the tumor rate for mice in the second class fell below that of the first class. From parents free from lung tumors there were 34 non-tumor and 15 lung tumor mice, or 31 per cent. The number of offspring in cases in which one of the parents had a lung tumor was small. There were 16 mice without lung tumors and 6 mice which developed them, or 27 per cent. From crosses between 2 parents with lung tumor there were fewer individuals (5) without lung tumor than there were with lung tumor (8). The numbers in the age period from 31 to 36 months are small but the percentage of tumors increases from the first to the third class.

Among the males, the numbers in the several age periods are small

but the percentages are consistently higher in the second and third classes except in the age period of 31 to 36 months. The largest groups are found between 19 and 24 months of age. From parents free from tumor (Class 1) there were 24 non-tumor to 10 tumor mice (29 per cent); from parents one of which had a tumor (Class 2) there were 10 non-tumor to 14 tumor mice (58 per cent); there were 4 mice from parents both of which had tumor and 3 out of the 4 were tumor mice.

The two inbred strains—the Bagg albinos and Strain 1194—have not been included in the above figures. The distribution of the indi-

Females of Strain 1194

Type of mating	Age, 13-18 mos.		19-24 mos.		25-30 mos.		Total	
	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor
0 × 0	68	2	40	1	15	1	123	4
T × 0	6	0	6	1	0	0	12	1

Males of Strain 1194

Type of mating	Age, 13-18 mos.		19-24 mos.		25-30 mos.		Total	
	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor
0 × 0	13	0	18	3	16	4	47	7
T × 0	5	0	0	0	0	0	5	0

0 × 0 total for males and females = 170 no tumor to 11 tumor
T × 0 " " " " " = 17 " " = 1 "

0 × 0 = neither parent with tumor
T × 0 = one " "

TEXT-FIG. 7.

viduals according to age, sex, and class is shown in Text-figs. 7 and 8. In Strain 1194 the majority of the matings were between parents in which no tumor was found. Of their offspring (males and females) there were 170 which did not develop lung tumors and 11 which did develop tumors, giving a tumor rate of 6 per cent. Of the 18 offspring from matings between tumor and non-tumor parents only one developed a growth in the lung. There were no matings between 2 tumor mice. In the Bagg strain, from non-tumor parents there were 2 non-tumor mice and one individual with a tumor. From crosses in which one parent had a tumor the ratio was 15 non-tumor and 15 tumor mice and

from matings in which both parents had lung tumors the ratio was 5 to 6. In these strains little difference is seen in the ratios from the various types of crosses.

If the available data are combined it is found that among the offspring of both sexes from non-tumor parentage there was a total of 465 mice of which 86 developed lung tumors (19 per cent); from parents one of which had tumor, there were 205 mice of which 81 developed tumors (40 per cent) and from doubly cancerous parentage

Females of Bagg strain

Type of mating	Age, 13-18 mos.		19-24 mos.		25-30 mos.		Total	
	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor
0 × 0	0	0	0	1	0	0	0	1
T × 0	2	1	6	4	3	4	11	9
T × T	0	2	0	0	5	4	5	6

Males of Bagg strain

Type of mating	Age, 13-18 mos.		19-24 mos.		25-30 mos.		Total	
	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor	No tumor	Tumor
0 × 0	0	0	1	0	1	0	2	0
T × 0	0	1	1	2	3	3	4	6
T × T	0	0	0	0	0	0	0	0

0 × 0 total for males and females = 2 no tumor to 1 tumor
T × 0 " " " " " = 15 " " = 15 "
T × T " " " " " = 5 " " = 6 "

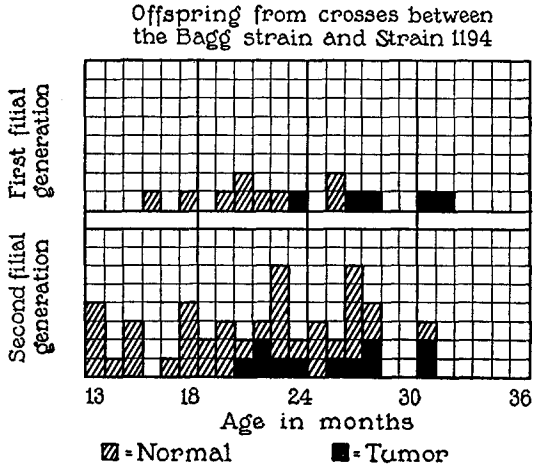
0 × 0 = neither parent with tumor
T × 0 = one parent with tumor
T × T = both parents with tumor

TEXT-FIG. 8.

there were 61 progeny of which 29 had tumors (48 per cent). These totals and the figures given in the separate analyses show that mice are more likely to have lung tumors when one of their parents had a lung tumor than if neither parent did and this likelihood is increased still further when both parents have tumors.

4. Crosses between Strains Having a High and a Low Incidence of Tumors of the Lung.—There were a few matings between males from the Bagg strain which has a lung tumor incidence of 37.0 per cent and females from Strain 1194 in which the lung tumor incidence is 6.7

per cent. Only one of the 2 males used developed a tumor. None of the females had growths in the lung. Of the 14 members of the first filial generation which lived to be at least 16 months old, 7 sons were free from lung tumors while 5 developed them. Neither of the 2 daughters had lung tumor though one lived to be 16 and the other 18 months old. These individuals and several more which died before tumor age were inbred to produce the second filial generation. The males of this second generation were used in another experiment since their value for the lung tumor record was at that time unknown. Of the females 49 lived to be more than 12 months old and of them 11 (22 per cent) developed lung tumors. The age distributions of the



TEXT-FIG. 9.

first and second filial generations are represented in Text-fig. 9. In the first filial generation most of the non-tumor mice were younger than the individuals with tumor. The appearance of tumors in the first generation when tumor-free individuals from a low tumor stock were crossed with mice from a high tumor stock suggests that tumor susceptibility is dominant.

SUMMARY AND DISCUSSION.

1. The occurrence of tumors in the lung in mice is dependent to a certain extent upon the age of the individual. No tumors were found

in the lungs of mice less than 8 months old. They occurred with greatest frequency in mice of about 24 months or older. Mice may live to be more than 3 years old without developing growths in the lung. These facts show that the development of tumors of the lung, if hereditary, is a variable character. An individual, genetically a tumor mouse, may live to a great age without showing a tumor if the requisite environmental stimulus (external or internal) is lacking.

Sex if effective at all has a comparatively slight influence upon the incidence of lung tumors.

2. Two strains of mice were studied which exhibit differences in their rates of incidence of lung tumors that are large enough to be significant. The conflict in the evidence from different laboratories as to whether or not tumors of the lung are the commonest type found in mice, is probably to be explained on the basis of a differing hereditary tendency to such growths in differing stocks.

3. Data from a number of sources indicate that offspring from parents free from lung tumors have a lower rate of lung tumor incidence than offspring from parents one of which had a tumor. If both parents had lung tumors the rate of tumor incidence among their offspring is increased still further.

4. In crosses between mice from strains which have high and low rates of incidence of lung tumor, tumors appeared in about half of the individuals of the first generation and in about one-quarter of the second generation. If the character responsible for the development of the growths is recessive it should not be found in the first filial generation unless both parents are carrying it. There is no proof that the female parents did not carry it but since they were taken from a strain in which the incidence of the growths was but 6.7 per cent the chances seem good that they were free from it. This suggests that the character determining the incidence of pulmonary tumors may be a dominant one.

A dominant character is not expected to appear among the offspring from parents neither of which has shown the character. The numerous instances which have been tabulated in this paper of mice with lung tumors among the offspring of parents free from lung tumors, must be explained on the assumption that tumor susceptibility is not

only dominant but variable and that some of the parents which did not actually develop tumors were genetically tumor mice and had the capacity for developing tumors although it was not brought out. As we have already concluded on the basis of the relationship between age and tumor incidence that susceptibility to the development of lung tumors is a variable character our explanation of the occurrence of tumor mice derived from tumor-free parents is justifiable.

The existence of strains of mice with rates of incidence of lung tumors that differ as widely as do the two that we have studied, the relatively high incidence of pulmonary growths among mice of tumor parentage as compared with mice from non-tumor parents, and the fact that females from a strain in which pulmonary tumors are rare when crossed with individuals from a strain in which they are frequent give a fairly high rate of incidence of the growths among the first and second filial generations,—all these facts indicate that susceptibility to the development of tumors in the lung is an inherited character.