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FURTHER INVESTIGATIONS ON THE ORIGIN OF TUMORS IN MICE.

I. Tumor Incidence and Tumor Age in Various Strains of Mice.

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The starting point for our investigations was the observation of the endemic occurrence of tumors in animals.[1]

At that time, as well as on later occasions, we emphasized the fact that hereditary factors might be the cause of this endemic occurrence and that we had not been able to find any direct indication of infection; and we had furthermore occasion in a later publication to point out the importance of analyzing these conditions through breeding experiments. In 1907 we published some observations made at the mouse farm of Miss Lathrop, in Granby, Mass., which rendered it probable that the frequency of tumors in mice at certain places was in all probability due, not to infection, but to hereditary transmission in certain families.[2] Keeping mice in cages, where formerly tumor mice had lived, did not increase the ratio of cancer among those mice, while there was some indication that mice belonging to different families and kept on the same farm in Granby, Mass., showed a different tumor incidence, although the living conditions were approximately the same for the various families.

In 1910 we were enabled to resume these investigations on a larger scale on the same mouse farm in Granby, and in the following year we published the tree of one of the families of mice under our observation in which the hereditary transmission of tumors had been apparent.[3] Since our publication in 1907 there

[1] Loeb, L., On Carcinoma in Cattle, *Medicine,* 1900, vi, 286. Ueber das endemische Vorkommen des Krebses beim Tiere, *Centralbl. f. Bakteriol., 1te Abt., Orig.,* 1904, xxxvii, 235.

[2] Loeb, Further Observations on the Endemic Occurrence of Carcinoma, and on the Inoculability of Tumors, *Univ. Penn. Med. Bull.,* 1907–08, xx, 2.

[3] Loeb, Ueber einen Kontakt-Kombinationstumor bei einer weissen Maus, *Centralbl. f. allg. Path.,* 1911, xxii, 993.

appeared two investigations, one by Tyzzer[4] and a more recent one by Murray,[5] dealing with the heredity of tumors in mice. Both compared the frequency of tumors in a certain number of mice which were directly descended from tumor mice with those which had no tumor mice in their immediate ancestry. Tyzzer considers that his results suggest a possible influence of heredity, and Murray also considers his conclusions not yet as quite definite. Inasmuch as the results of Murray are more recent and are based on more extensive observations than those of Tyzzer, it might be of interest to analyze briefly the facts on which Murray's conclusions are based. Murray states that all the mice concerned in the experiments are descended ultimately from animals known to have suffered from cancer. "When new spontaneous cases of cancer in mice bred outside the laboratory are obtained, males bred in the laboratory from cancerous stock are mated with them, and as time goes on the process is repeated, so that a large number of animals with a composite known ancestry is obtained. This continual introduction of fresh cancerous stock to the parentage was decided on to eliminate, as far as possible, the influence of other indeterminate peculiarities which might conceivably influence the incidence of cancer indirectly in the nearly related animals derived by inbreeding from a single pair." Murray based his conclusions on the observation of 562 females which attained the age of 6 months or more. These 562 mice were divided into two unequal groups, one in which cancer occurred either in the mother, one or the other grandmother, or in all three, and another in which cancer was more remote in the ancestry. In the first lot of mice 18.2 per cent, in the latter 8.2 per cent tumor mice were found.

The principal criticism which can be made against conclusions based on this procedure is the following: Mice whose mothers or grandmothers had no tumors might belong to strains rich in tumors. In this case their offspring would in all likelihood develop many tumors, while mice whose direct ancestry had tumors might belong to strains very poor in tumors and their offspring would then develop less tumors than the offspring of non-tumor mice. For instance, if we should select non-cancerous female mice from our strains "English," "8½ plus English," "Michigan Wild plus 101," "Nov. 3d Strain," "Nov. 8th Strain," and compare the cancer rate of their offspring with the cancer rate of tumor mice from the strains "8½," "London," "Heitler," "Silver," "Cream," "German plus Carter," we would find that the offspring of the non-tumorous females is much richer in tumors than the offspring of tumorous animals. There is therefore a very large factor of chance in the results obtained by Murray. Accidentally the mice whose grandparents or parents had had tumors belonged to strains somewhat richer in tumors than the strains to which the other mice belonged. Definite conclusions can only be obtained if we use strains the tumor rate of which is known. These results we published in 1913.[6] We showed

[4] Tyzzer, E. E., A Series of 20 Spontaneous Tumors in Mice, with the Accompanying Pathological Changes and the Results of the Inoculation of Certain of These Tumors into Normal Mice, *Jour. Med. Research,* 1907–08, xvii, 155.

[5] Murray, J. A., Cancerous Ancestry and the Incidence of Cancer in Mice, *Fourth Scientific Report of the Imperial Cancer Research Fund,* 1911, 114.

[6] Lathrop, A. E. C., and Loeb, L., The Incidence of Cancer in Various Strains of Mice, *Proc. Soc. Exper. Biol. and Med.,* 1913, xi, 34. Loeb, L., Some Recent Results of Cancer Investigations, *Lancet-Clinic,* 1913, cx, 664.

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among other facts on the basis of very extensive observations that different strains kept at the same farm differed markedly in their tumor rate, that this difference in tumor rate was a characteristic which was maintained approximately constant through several generations, and we gave definite figures for the frequency of tumors in different strains. Thus the great importance of the factor of heredity in the transmission of tumors in mice was definitely proven.

Since 1913 we have continued our investigations and we wish to report (1) the extension of the work, (2) more detailed figures concerning the cancer rate and cancer age in the successive generations of the various strains, and (3) some new facts especially regarding the relation between cancer rate and cancer age. These data will also form a basis for succeeding communications.

We found it best to divide the mice into three classes, according to age: (1) in Class I were mice 7, 8, 9, 10, 11, and 12 months old; (2) in Class II were mice 13, 14, 15, 16, and 17 months old; (3) in Class III were mice 18 months old and older. Mice dead without tumor below the age of seven months are disregarded. In our tables we give the generations of the mice as F_1, F_2, F_3, and so on, designating as F_1 the first generation which we included in our new records. On the left side of the table we state the number of mice that die without tumors, on the right side those with tumors. First we give the total figure of observed mice, then in brackets the number of mice that die in each of the three periods of life. The Roman figures after each Arabic figure indicate the period of age during which a certain number of mice died. We give first the absolute figures and below in each case the percentage figures. In the summary of the various strains we add the percentage of mice dying with and without tumors in the respective periods expressed in per cent of the total number of mice dying in this period. We considered only female mice and included all the subcutaneous tumors. The large majority of these are the common adenocarcinomata and carcinomata. There occur a few other tumors, as, for instance, squamous cell carcinoma and sarcoma. The number of these latter tumors is, however, in our material apparently so small that the results cannot be affected by including all the subcutaneous tumors in our calculations. Tumors of internal organs were disregarded at present. We shall report on this phase of our work on a

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later occasion after the microscopic study has been concluded. Macroscopically visible tumors in internal organs of mice are of little significance for our present studies. While the material on which our conclusions are based is great, we intend to continue our work, and if there should be an error in our conclusions, it will in all probability be cleared up by our further experiments.

I. Tumor Incidence and Tumor Age of Non-Hybrid Strains.

In this class we consider strains, which, though of composite origin, were kept inbred in our experiments for a number of generations.

1. Strain English.

These are mice imported from England in 1905. Their offspring were brought to Granby, Mass., in the spring of 1906. The mice have a dull reddish color and their offspring have various colors, especially sable, agouti, and dull reddish. Later another female mouse of the same English strain with a bright red color is added. By breeding various red colored mice together an attempt is made to obtain red stock. However, among the offspring there are many black, sable, agouti, and chocolate colored animals, but rarely a mouse with a good red color. All the mice belonging to this strain were derived from a very small number of animals. The strain had been propagated for a number of years at the time when we started our experiments. The same holds good in the case of the majority of other strains. It may have been different in those strains which had been more recently imported, as the "European" and "German," "Heitler" and "London." But even in the Heitler and London the fact that the results even in small groups are, on the whole, concordant with each other does not make it probable that the various individuals within a strain which we used for propagation represented very different kinds of mice. Selection among the original gave, after breeding through several generations, a strain with a good proportion of black-eyed tans, and another with a small proportion of good black-eyed reds. There were also occasionally pink-eyed mice in these groups. One pink-eyed reddish tan colored male of English origin was mated to white females of Massachusetts origin. The offspring of this group again showed various colors, some of them white. These whites bred together for one generation gave again pure white offspring. The other offspring of the reddish tan male and white Massachusetts females were mostly black and sable in color. They all had black eyes. The latter when bred together without selection had generally dull colored offspring, but there were a very small number with pink eyes and a reddish or tan color, and two or three of a dull bluish smoke shade. These various pink-eyed animals had all pink-eyed offspring, usually of a non-characteristic color in the first generation, but in the succeeding generations the clear tan shade appeared; these tan mice, when bred together, bred true. Their offspring were the only mice which had exactly this color. These tan colored

mice gave origin to the English substrains "101" and "Tan." The latter are mostly the offspring of Tumor Mice 121 and 122. They had therefore all tan color. Other mice of the same origin had, as mentioned above, a dull bluish color; there were two or three of those among the grandchildren of the original pink-eyed reddish tan male and the white Massachusetts female. These bluish mice bred together had some offspring of the same color and a few with distinct silver color. The silver colored were rare at first. Mice with somewhat similar, approximately silver color occurred also occasionally among the original English mice, which had no admixture of white Massachusetts stock. Through several generations these silver mice were added to the silver mice of the mixed origin. These silver mice selected and interbred gradually bred true. Occasionally, however, there occurred among them some mice of lighter, almost silver fawn color. The latter bred together also breed true and have only silver fawn offspring. Thus we have four distinct substrains of the English strains, which are characterized by their color which remains distinct: (1) the "Tan" mice with pink eyes, mainly offspring of Tumor Mice 121 and 122; (2) the substrain "101," also tan mice; (3) the "Silver"; and (4) the "Silver Fawn."

In addition to those we have two substrains in which mice of various colors occur: (1) "English Sable," members of the original English family. One pair of sable color was selected and gave origin to this substrain. This substrain has never had mice with the red and tan colors which some of the original English mice showed, but had many sable, some black, and many white mice. As white males were usually kept, the colored mice have now become eliminated and all "Sable" are at the present time white. The colored mice belonging to this substrain have never had pink eyes, but the white mice at present are pink-eyed, like ordinary white mice. (2), The last substrain is "English A," non-selected groups from the general stock. There were some groups all sable in color, some all red or orange; in other groups various colors were represented, sable, agouti, black, white, dull tans, and dull reds. In no case, however, did a real Silver occur in such a mixed group. They occurred only a few times in earlier generations and were either discarded if of dull color, or added to the first two Silver generations, if of fairly clear color. Mice in this strain differed not only in their color, but also in their resistance. On the whole, the red and yellow pink-eyed varieties of English mice are not very rugged and not satisfactory as breeders. The females of the 101 strain were prolific, they very frequently had new litters, but they were usually small and died often at early ages. All the Silver as well as the 101 and Tan had pink eyes. None among the English Sable, with the exception of the white ones, had pink eyes. Of the substrain A some had pink eyes, but the majority were black-eyed. No. 481 a and her descendants had pink eyes, although they are mice of a relatively dark, dull agouti color.

The following substrains were thus distinguished:

1. English A, composed of various groups of English, not line bred.
2. Family 101, the offspring of pink-eyed tans.
3. English Tan E, the offspring of Tumor Mice 121 and 122.
4. English Sable.

5. English Silver.
6. English Silver Fawn.

It was of special interest to compare the tumor rates in the various groups which had a similar origin and to determine whether the various groups differed markedly in their tumor rates.

(a) Earlier groups.

1. Substrain English A.

Without tumors.	With tumors.
44 (33 I 4 II 7 III)	71 (25 I 39 II 7 III)
37% (75% I 9% II 16% III)	63% (35% I 55% II 10% III)

(b) Later groups.

12 (7 I 5 II)	21 (13 I 7 II 1 III)
36% (58% I 42% II)	64% (62% I 33% II 5% III)

(c) Additional records (winter, 1914–15).

8 (3 I 4 II 1 III)	19 (14 I 5 II)
30% (38% I 50% II 12% III)	70% (79% I 21% II)

We see that the tumor rate in the same group at different periods remained approximately the same (63, 64, and 70 per cent), that a large per cent of the tumors appear in the first period of life, and a large part of the remaining tumors in the second period. As a result of the high tumor incidence in young mice, the mortality is in early life so great that the number of mice attaining an old age is relatively small.

The figures for the total of this lot are:

Without tumors.	With tumors.
64 (43 I 13 II 8 III)	111 (52 I 51 II 8 III)
37% (67½% I 20% II 12½% III)	63% (47% I 46% II 7% III)
II + III 26% III 50% I + II 35% I 35%	II + III 74% III 50% I + II 65% I 65%

In two cases the offspring of tumor mice belonging to this group were followed separately. Through four generations the offspring of Tumor Mouse 481 a, (dull agouti with pink eyes) were recorded.

Without tumors.	With tumors.
3 (3 I)	11 (8 I 3 II)
21% (100% I)	79% (72% I 28% II)

In this case the result is in accordance with the behavior of the group as a whole.

In the offspring of Tumor Mouse 281, which were followed through five generations, the tumor rate is very much lower.

(a) Earlier generation.

Without tumors.	With tumors.
7 (7 I)	1 (1 II)

(b) Later generations.

5 (1 I 3 II 1 III)	2 (1 I 1 II)
Total: 12 (8 I 3 II 1 III)	3 (1 I 2 II)
80% (68% I 24% II 8% III)	20% (34% I 66% II)

It is possible that we accidentally isolated in this last family recessives with a low tumor rate. But as the mice died early in this case, and the number of animals we observed is small, we must leave this question at present undecided.

2. Substrain Family 101.

No. 101 was a pink-eyed English Tan tumor mouse from a family in which all three females had tumors.

	Without tumors.	With tumors.
F_1	3 (3 I)	
F_2	6 (6 I)	10 (9 I 1 II)
	37% (100% I)	63% (90% I 10% II)
F_3	7 (3 I 4 II)	22 (17 I 5 II)
	24% (43% I 57% II)	76% (77% I 23% II)
F_4	9 (5 I 4 II)	27 (17 I 9 II 1 III)
	25% (55% I 45% II)	75% (63% I 33% II 4% III)
F_5	2 (1 I 1 II)	6 (1 I 5 II)
	25% (50% I 50% II)	75% (17% I 83% II)
F_6	2 (2 I)	5 (2 I 3 II)
	28% (100% I)	72% (40% I 60% II)
Total:	29 (20 I 9 II)	70 (46 I 23 II 1 III)
	29% (69% I 31% II)	71% (66% I 33% II 1% III)
II + III	28% I 30% I + II 29%	II + III 72% I 70% I + II 71%

We see that we have here to deal with a high tumor rate (71 per cent), that the majority of the tumors appear in the first period of life, and the rest in the second period, and furthermore that in the six generations which we observed in this family the tumor rate and

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the tumor age were about the same. If we disregard the mice dying in the first period of life, the tumor incidence remains about the same (72 per cent). In this family a tumor was observed to appear in a six months old mouse.

3. Substrain English Tan E.

Offspring (pink-eyed) of two early Tan Tumor Mice 121 and 122.

Without tumors.	With tumors.
3 (3 I)	8 (6 I 2 II)
27% (100% I)	73% (75% I 25% II)

This is a small group of similar character to the preceding family. Here tumor incidence and tumor age are similar to those in 101.

4. Substrain English Sable.

(a) Older records.

	Without tumors.	With tumors.
F_1	3 (2 or 3 I 1 uncertain II)	6 (3 I 3 II)
F_2	12 (11 I (6 of these below 6 months) 1 III)	40 (33 I 5 II 2 III)
F_3	11 (8 I 1 II 2 III)	25 (21 I 3 II 1 III)
F_4	3 (1 I 2 II)	21 (17 I 3 II 1 III)
F_5	0	5 (4 I 1 II)
Total:	29 (22 I 4 II 3 III)	97 (78 I 15 II 4 III)
	23% (76% I 14% II 10% III)	77% (81% I 15% II 4% III)
	II + III 29%	II + III 71%

(b) Newer records.

F_2	2 (1 I 1 II)	5 (3 I 2 II)
F_3	19 (11 I 7 II 1 III)	24 (14 I 8 II 2 III)
F_4	4 (3 I 1 II)	4 (1 I 3 II)
Offspring of Tumor Mouse 217	1 (1 I)	6 (2 I 4 II)
Total:	26 (16 I 9 II 1 III)	39 (20 I 17 II 2 III)
	40% (62% I 34% II 4% III)	60% (51% I 44% II 5% III)
	II + III 34%	II + III 60%

Total of (a) and (b):

55 (38 I 13 II 4 III)	136 (98 I 32 II 6 III)
28% (69% I 24% II 7% III)	72% (73% I 23% II 4% III)
II + III 31%	II + III 69%

(c) Family of Tumor Mouse 437. (No. 437 raised young while she had a tumor.)

F_1 1 (1 I)	7 (1 I 6 II)
F_2 2 (2 I)	4 (2 I 2 II)
F_3 2 (2 I)	5 (4 I 1 II)
F_4 0	
Total: 5 (5 I)	16 (7 I 9 II)
24% (100% I)	76% (44% I 56% II)

(d) Additional records (winter, 1914–15).

F_3 9 (4 I 3 II 2 III)	15 (5 I 4 II 6 III)
F_5 7 (2 I 3 II 2 III)	8 (4 I 3 II 1 III)
F_6 0	1 (1 I)
Total: 16 (6 I 6 II 4 III)	24 (10 I 7 II 7 III)
40% (37½% I 37½% II 25% III)	60% (42% I 29% II 29% III)
Total of English Sable:	176 (115 I 48 II 13 III)
76 (49 I 19 II 8 III)	70% (66% I 27% II 7% III)
30% (65% I 25% II 10% III)	II + III 69% III 62% I 70% I + II 71%
II + III 31% III 38% I 30% I + II 29%	

If we compare the total of English Sable with the total of English 101, we see that the figures are very similar as to the incidence of cancer and the age at which cancer appears. In both cases (without consideration of the mice alive in the various periods) the majority of tumors appear in the first period of life. In English A the tumor incidence is only slightly less, and here also the first period of life is the one in which there appear more tumors than in any other period; but here again the preponderance of the first period over the other periods is not so great as in the case of the Sable and 101. English Tan and English Sable are similar. Within the Sable the various generations and families of individual tumor mice behave in a similar way as the total. Of course, certain variations occur, but they are relatively slight and they are especially noticeable where the number of observed mice is relatively small; only in one family a different tumor rate may prevail, but even here it is not certain. The offspring of mice born while the mother had a tumor are not more liable to have tumors than other mice of the same group (family of Tumor Mouse 437). On the whole, the variations in the incidence of tumors and the age at which they appear follow a parallel course; if the incidence is somewhat lower in a group, the tumors also appear at a somewhat later period of life. At least this parallelism is noticeable in the records within the groups of the English strain just mentioned. It remains to be seen whether or not this parallelism is accidental.

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5. Substrain English Silver.

They were bred for color. All the English Silver mice are poor breeders.

(a) Older records.

Without tumors.	With tumors.
74 (29 I 39 II 6 III)	5 (1 I 4 II)
94% (39% I 53% II 8% III)	6% (20% I 80% II)
II + III 92%	II + III 8%

There were 9 groups. In 7 no tumors were observed, in 2 groups tumors appeared. In 1 of these 2 groups 2 out of 21 mice, in the other 3 out of 13, had tumors.

(b) Additional records (winter, 1914–15).

35 (15 I 10 II 10 III)	3 (3 I)
92% (43% I 28½% II 28½% III)	8% (100% I)

Here tumors appeared in 2 groups out of 6. In one there were 2 tumor mice in a group of 10, in the other 1 out of 7 had a tumor.

Total of all English Silver:

109 (44 I 49 II 16 III)	8 (4 I 4 II)
93% (41% I 45% II 14% III)	7% (50% I 50% II)

We see that tumor incidence is the same in both sets (a) and (b). The difference between the other English and the English Silver is most striking. In the latter the tumor rate is very low throughout. Furthermore, it is of interest that out of 15 groups tumors appeared in only 4, and in 3 out of these 4 groups there were more than 1 tumor mouse, while in 11 groups no tumor appeared.

Of great interest is the fact that while the tumor incidence in the English Silver is very low, the mice that had tumors had them at about as early an age as the strains with high tumor rate. The English Silver that did not have tumors in the first or second period of life were not more liable to acquire them in the third period than they were in the first and second periods. It seems therefore that incidence of tumor and tumor age are unit factors which are to some extent independent and transmitted independently of each other. Furthermore, we see here established the interesting fact that there is a linking in this case between the color of the mice and the rate of tumor incidence. A low rate goes with a silver color, while a high rate goes with the sable, tan, and white among the English strains.

6. Substrain English Silver Fawn.

The Silver Fawn have been more prolific than the Silver, but just as delicate. They rarely raise their young. Two groups were kept: (1) 1 to 9 months old, 2 to 11 months old, 1 to 13 months old, 1 to 15 months old, without tumors; (2) their offspring, 1 to 9 months old, 2 to 12 months old, 3 to 13 months old, 2 to 16 months old, without tumors. This record makes it probable that tumors are here as rare as among the Silver. We have therefore split off from the English strain a substrain Silver, in which there went hand in hand with the color a a very low tumor incidence. And from the Silver again another variety of color, Silver Fawn, was split off, in which again there was linked with the color a low tumor incidence.

2. Strain "Cream."

The mice that gave origin to this strain were obtained in the year 1903 from two different sources, Atlantic City and Springfield, Ohio. Up to the year 1911 only the cream colored mice were kept and used for breeding, while the black and sable colored mice which appeared more frequently were discarded. From 1911 on, females of all colors were kept. The females in this strain are poor breeders; the mice grow slowly, but ultimately reach the same size as the other mice. Many of these mice reach old age.

(a) Older records.

Without tumors.	With tumors.
127 (35 I 50 II 42 III)	3 (1 II 2 III)
98% (27% I 39% II 34% III)	2% (33% II 66% III)
II + III 97% III 97.6%	II + III 3% III 2.4%

There were 26 groups in this lot. In one group there appeared 2 tumor mice, and in another group 1 tumor mouse. In 24 groups there appeared no tumor mouse. As in the case of the English mice, the rate of tumor incidence is not essentially changed, if only mice in Periods II and III or mice in Period III of life are considered.

(b) Additional records (winter, 1914–15).

94 (28 I 41 II 25 III)	2 (1 II 1 III)
98% (29% I 44% II 27% III)	2% (50% II 50% III)

These 2 tumor mice appeared in 2 different groups. The tumor incidence is here the same as in Group (a). The low tumor rate in this strain is therefore a constant condition.

Total Cream strain:	
221 (63 I 91 II 67 III)	5 (2 II 3 III)
98% (29% I 41% II 30% III)	2% (40% II 60% III)
II + III 97% III 96%	II + III 3% III 4%

The tumor rate is extremely low, 2 per cent. If we leave the mice dying in the first or first and second period of life out of consideration, the tumor rate is not essentially changed.

Cream X.

Seven mice of the Cream strain (with black, cream, and sable color) were separated from the others, and four generations of these mice were bred. They were called Cream X.

(a) Older records of Cream X.

Without tumors.	With tumors.
44 (20 I 13 II 11 III)	0
100% (45% I 30% II 25% III)	0

(b) Recent records.

86 (28 I 32 II 26 III)	5 (2 I 3 II)
94½% (33% I 37% II 30% III)	5½% (40% I 60% II)
Total of Cream X:	
130 (48 I 45 II 37 III)	5 (2 I 3 II)
96% (37% I 35% II 28% III)	4% (40% I 60% II)

Thus the tumor rate in the Cream X is of the same order as in the Cream, although they had been kept entirely separate. We may therefore conclude that in this case we have to deal with relatively pure strains as far as the tumor incidence is concerned. Of 14 groups of Cream X, 12 were free from tumors; in each of 2 groups (holding 9 and 7 mice respectively) 2 tumor mice were found. If we arrange the Cream X according to generations, we find the following:

F_1 34 (13 I 12 II 9 III)	
100% (38% I 35% II 27% III)	
F_2 39 (15 I 12 II 12 III)	
100% (38% I 31% II 31% III)	
F_3 39 (14 I 12 II 13 III)	5 (1 I 3 II)
89% (36% I 31% II 33% III)	11% (20% I 80% III)
F_4 18 (6 I 9 II 3 III)	1 (1 I)
95% (33% I 50% II 17% III)	5% (100% I)

Taking Cream and Cream X together we find that tumors occur here apparently later than in the English strain, also later than in the Silver; absolutely the majority of tumors appear here in the second and not in the third period of life.

3. Strain No. 8.

No. 8 is of mixed origin. They are in part descended from mice received from Springfield, Mass., and from Ohio; in part from a pair of plum-silver mice sometime imported from England, but not related to the English strain mentioned previously. From this mixed origin descended some plum-silver females which were in Dec., 1907, mated with the son of a tumor mouse found in Granby. Their descendants are the No. 8 strain. The male, the son of a tumor mouse, was later, when he had grown old, left to his daughters and gave origin to the strain designated 8½. No. 8 is a strain which breeds well and is healthy; the mice live longer than the English strain.

(a) Older records of No. 8.

	Without tumors.	With tumors.
F_2	1 (1 III)	4 (4 III)
F_3	14 (2 I 3 II 9 unknown age)	8 (3 I 2 II 3 III)
F_4	24 (22 I 1 II 1 III)	11 (3 I 6 II 2 III)
F_5	18 (9 I 9 III)	9 (4 I 2 II 3 III)
F_6	39 (8 I 15 II 16 III)	17 (7 I 8 II 2 III)
F_7	29 (19 I 8 II 2 III)	3 (1 II 2 III)
F_8	12 (7 I 3 II 2 III)	4 (1 II 3 III)
F_{10}	12 (3 I 3 II 6 III)	8 (4 II 4 III)
Total:		
	149 (70 I 33 II 37 III 9 unknown age)	64 (17 I 24 II 23 III)
	70% (47% I 22% II 31% III)	
	II + III 60% III 62%	30% (26% I 37% II 37% III)
		II + III 40% III 38%

In this group is maintained through the various generations a medium tumor rate, considerably lower than in the English strain, and the tumor age is higher; also higher than in the English Silver, which have a considerably lower tumor rate than the No. 8 strain.

(b) One tumor mouse, No. 100, from the fourth generation of the No. 8 strain was mated with a male of No. 8, F_4 and had the following offspring:

F_1	0	3 (2 II 1 III)
F_2	4 (1 I 3 III)	6 (1 I 4 II 1 III)
F_3	5 (5 I)	0
F_4	3 (2 I 1 II)	6 (6 I)
Total:		
	12 (8 I 1 II 3 III)	15 (7 I 6 II 2 III)
	44% (67% I 8% II 25% III)	56% (74% I 40% II 13% III)

The tumor rate is here apparently higher than in the No. 8 strain, and the tumor age somewhat lower.

(c) Additional records (winter, 1914–15).

F_8	26 (7 I 13 II 6 III)	2 (2 III)

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In the 8th generation the tumor rate is lower than usual. The two tumors appeared here in the last period of life. We have in this case to deal with a relatively small number of mice. Until further observations indicate a constancy in the general lowering of the tumor rate in this strain, we cannot attach too much importance to this observation.

Total of No. 8:	
187 (85 I 47 II 46 III 9 unknown age)	81 (24 I 30 II 27 III)
70% (45% I 24% II 24% III)	30% (29% I 37% II 34% III)
II + III 62% III 63%	II + III 38% III 37%

In this case the tumor rate increases somewhat if we consider only the mice in the second and third periods of life.

4. Strain 8 1/2.

This is a strain closely related to Strain 8. The male (son of a tumor mouse) which gave origin to No. 8 was mated to his daughters, which latter belonged to the No. 8 strain. This strain is less rich in tumors than No. 8, and the tumors appear also at a rather late period of life. This fact may be explained by assuming that the male in this case belonged to a strain less rich in tumors than the females.

Without tumors.	With tumors.
$F_1 + F_2$ 24 (10 I 14 II)	1 (1 II)
F_3 14 (6 II 8 III)	4 (2 I 1 II 1 III)
F_4 51 (14 I 18 II 19 III)	1 (1 II)
F_5 40 (17 I 14 II 9 III)	6 (6 II)
F_6 2 (2 I)	0
Total:	
131 (43 I 52 II 36 III)	27 (6 I 17 II 4 III)
83% (33% I 40% II 27% III)	17% (22% I 63% II 15% III)
II + III 81% III 90%	II + III 19% III 10%

Leaving out of consideration mice which did not reach the second or third period of life modifies the figures only slightly without essentially changing the results.

5. Strain Carter.

This strain is the offspring of a son of a pink-eyed English tumor mouse of orange color and of 9 females (7 of which were white, 2 brown with white spots) obtained in Utica, N. Y. The females of this strain are as good breeders as the average No. 8 or English, but do not grow up as fast as the latter.

Without tumors.	With tumors.
F_1 1 (1 III)	
F_2 11 (5 I 2 II 4 III)	3 (2 II 1 III)
F_3 19 (7 I 7 II 5 III)	16 (8 I 5 II 3 III)
F_4 10 (3 I 3 II 4 III)	7 (4 I 2 II 1 III)

Total:	
41 (15 I 14 II 12 III)	26 (12 I 9 II 5 III)
61% (36% I 35% II 29% III)	39% (46% I 35% II 19% III)
II + III 65% III 71%	II + III 35% III 29%

Disregarding mice that died during the first period of life without tumors, but including those acquiring tumors during this period, the figures are: without tumors 50% (54% II 46% III); with tumors 50% (46% I 35% II 19% III). The tumor rate in this strain is higher than that of No. 8 and 8½ and lower than that of English. The tumor age is slightly higher than in the case of the English and lower than in Nos. 8 and 8½. Wherever the figures are sufficiently large in the various generations, the results are similar.

6. Strain European.

Thirteen mice of various sizes were imported from Europe, Feb., 1910. They are on the whole of smaller size than the Granby mice. They and their offspring suffer greatly from mouse typhus. In Oct., 1912, their number has not yet increased. Two of the offspring of the imported stock have tumors. Only a relatively small number of this lot lived long enough to be included in the records.

Without tumors.	With tumors.
F_4 7 (5 I 2 II)	0
F_5 9 (5 I 4 II)	2 (2 I)
Total:	
16 (10 I 6 II)	3 (2 I 1 II)
84% (62% I 38% II)	16% (66% I 34% II)

Substrain European from Trio.

Two females and one male (all probably of one litter) were separated from the rest of the European mice; one of these two females had a tumor when not yet quite a year old (No. 228). The offspring of these mice were more healthy, but here also occasionally typhus appeared.

Without tumors.	With tumors.
F_2 5 (1 I 3 II 1 III)	1 (1 II)
F_3 18 (6 II 12 III)	2 (1 II 1 III)
F_4 49 (23 I 14 II 12 III)	11 (5 I 4 II 2 III)
F_5 7 (3 I 4 II)	1 (1 II)
Total:	
79 (27 I 27 II 25 III)	15 (5 I 7 II 3 III)
84% (34% I 34% II 32% III)	16% (33% I 47% II 20% III)
II + III 84%	II + III 16%

The same tumor rate occurs here as in the other European group, notwithstanding the much larger number of mice in this group. The figures in both substrains are therefore confirmatory of each other. The tumor rate is similar to that in No. 8½. The tumor age is somewhat lower than that of No. 8 and No. 8½. The results in the various generations agree fairly well with each other.

7. Strain German.

These mice were imported from Germany in May, 1910. They are somewhat smaller than the average Granby mice, but a little larger than the European. They are a very prolific strain, but again die early on account of disease. Three just weaned young females and one male were the only ones to thrive. All the mice recorded are the offspring of these four mice.

	Without tumors.	With tumors.
F_1	0	3 (1 I 2 II or III)
F_2	0	2 (1 I 1 II or III)
F_4	6 (2 I 3 II 1 III)	3 (2 I 1 III)
F_5	0	2 (2 II)
F_6	4 (4 I)	
Total:		
	10 (6 I 3 II 1 III)	10 (3 I 5 II 2 III)
	50% (60% I 30% II 10% III)	50% (30% I 50% II 20% III)
	II + III 36%	II + III 64%

The number of mice is not large in this strain, but the indications are that we have to deal with a strain rich in tumors, which, however, do not appear as early as is the case of the English. In this lot the mortality in early life was great. The tumor rate increases, therefore, if we exclude the animals dying in the first period of life.

8. Strain Heitler.

This strain is the offspring of mice imported more recently from Germany.

	Without tumors.	With tumors.
F_1	13 (4 I 7 II 2 III)	3 (3 II)
	81% (31% I 54% II 15% III)	19% (100% II)
F_2	39 (24 I 5 II 10 III)	9 (1 I 8 II)
	81% (62% I 13% II 25% III)	19% (11% I 89% II)
F_3	13 (9 I 2 II 2 III)	11 (1 I 10 II)
	54% (70% I 15% II 15% III)	46% (9% I 91% II)
F_4	9 (5 I 4 II)	5 (2 I 3 II)
	64% (56% I 44% II)	36% (40% I 60% II)
Total:		
	74 (42 I 18 II 14 III)	28 (4 I 24 II)
	73% (56% I 24% II 20% III)	27% (14% I 86% II)
	II + III 57%	II + III 43%

In this strain the tumor rate as a whole is similar to that of No. 8. The tumor age also is similar, inasmuch as the first period of life is poor in tumors, even more so than in Nos. 8 and 8½. It is an interesting fact that in this strain the large majority of tumors appear in the second period of life, while the third period is free from tumors. For this reason the tumor rate increases, if we omit from consideration the mice dying in the first period of life, just as we did in the case of No. 8. On the whole, the figures are within certain limits similar in the different generations.

9. *Strain London.*

This strain comprises about a dozen animals with various colors imported from London, England, late in the summer of 1911.

Of five imported females, four had tumors.

(a) Older records.

	Without tumors.	With tumors.
F_1	22 (7 I 5 II 10 III)	9 (4 I 2 II 3 III)
F_2	19 (8 I 7 II 4 III)	7 (1 I 3 II 3 III)
Total:		
	41 (15 I 12 II 14 III)	16 (5 I 5 II 6 III)
	72% (37% I 29% II 34% III)	28% (31% I 31% II 38% III)
	II + III 73% III 70%	II + III 27% III 30%

(b) Family of an imported London mouse with tumor (481).

F_1	4 (3 I 1 III)	0
F_2	1 (1 II)	0
F_3	1 (1 I)	1 (1 I)

(c) Later records (winter, 1914–15).

F_1	9 (1 I 3 II 5 III)	3 (3 III)
F_2	16 (7 I 4 II 5 III)	2 (1 II 1 III)
F_3	15 (9 I 5 II 1 III)	11 (3 I 8 II)
Total:		
	40 (17 I 12 II 11 III)	16 (3 I 9 II 4 III)
	54% (42% I 30% II 28% III)	26% (19% I 56% II 25% III)
	II + III 64% III 54%	II + III 36% III 26%

Thus the later records agree very well with the former one, as to the rate of tumors and tumor age. The irregularities found in the individual generations increase in inverse ratio to the number of the

animals observed; but on the whole the variations are not very great. The tumor rate and tumor age are similar to those of No. 8. Omitting animals in the first or in the first and second period of life does not greatly alter the result.

Total:	
87 (36 I 25 II 26 III)	33 (9 I 14 II 10 III)
73% (41% I 29% II 30% III)	27% (27% I 43% II 30% III)

II. Tumor Incidence and Tumor Age of Some Hybrids.

These and a number of other strains, not yet mentioned, were used for hybridization and have thus produced a considerable number of additional strains which we observed through successive generations. Inasmuch as we shall report on the crosses later in connection with another problem, we shall here cite only a few of them.

1. German + Carter.

(a) Early records.

Without tumors.	With tumors.
195 (56 I 57 II 82 III)	15 (2 I 3 II 10 III)
93% (29% I 29% II 42% III)	7% (13% I 20% II 63% III)

(b) Later records.

131 (23 I 31 II 77 III)	17 (2 I 8 II 7 III)
88% (17% I 24% II 59% III)	12% (12% I 47% II 41% III)
Total:	
326 (79 I 88 II 159 III)	32 (4 I 11 II 17 III)
91% (24% I 24% II 52% III)	9% (12% I 34% II 54% III)
II + III 90% III 89% I 95% I + II 92%	II + III 10% III 11% I 5% I + II 8%

Hence the earlier and later records are similar in regard to the tumor rate as well as to the tumor age. The tumors appear very late. In the successive generations some variations occur; they are, however, on the whole not very great; the deviation from the mean is greatest where the number of observed mice is smallest. The tumors appear in all generations at a late period of life.

F_1 11 (6 I 5 III)	3 (3 III)
78% (55% I 45% III)	22% (100% III)
F_2 71 (15 I 18 II 38 III)	3 (3 III)
96% (21% I 25% II 54% III)	4% (100% III)

F_3 205 (49 I 48 II 108 III)	24 (3 I 10 II 11 III)
90% (24% I 23% II 53% III)	10% (13% I 42% II 45% III)
F_4 39 (9 I 22 II 8 III)	2 (1 I 1 II)
95.1% (20% I 60% II 20% III)	4.9% (50% I 50% II)

2. Silver + 10.

Without tumors.	With tumors.
F_1 1 (1 III)	3 (1 II 2 III)
F_2 40 (19 I 15 II 6 III)	17 (3 I 7 II 7 III)
70% (48% I 37% II 15% III)	30% (18% I 41% II 41% III)
F_3 95 (31 I 34 II 30 III)	52 (20 I 17 II 15 III)
65% (33% I 35% II 32% III)	35% (38% I 33% II 29% III)
F_4 13 (4 I 1 II 8 III)	8 (3 I 4 II 1 III)
62% (31% I 7% II 62% III)	38% (38% I 49% II 13% III)
F_5 1 (1 III)	4 (4 III)
Total:	
150 (54 I 50 II 46 III)	84 (26 I 29 II 29 III)
64% (35 2/3% I 33 1/3% II 31% III)	36% (32% I 34% II 34% III)
II + III 62% III 61%	II + III 38% III 39%

The various generations behave in a similar manner as far as tumor rate and tumor age are concerned. The tumors appear at a medium age.

3. European + No. 10 (Nov. 3d Strain).

The tumors appear in the successive generations at a similar rate. Variations occur especially if the number of mice is relatively small in a certain generation. The tumors appear on the average at a medium age in the various generations.

Without tumors.	With tumors.
F_1 1 (1 III)	1 (1 III)
F_2 5 (3 I 2 II)	16 (6 I 10 II)
24% (60% I 40% II)	76% (37% I 63% II)
F_3 21 (9 I 6 II 6 III)	75 (16 I 36 II 25 III)
22% (43% I 28% II 29% III)	78% (21% I 48% II 31% III)
F_4 42 (30 I 12 II)	71 (33 I 30 II 8 III)
37% (71% I 29% II)	67% (46% I 43% II 11% III)
F_5 2 (1 I 1 II)	20 (8 I 5 II 7 III)
9% 50% I 50% II)	91% (40% I 25% II 35% III)
Total:	
71 (43 I 21 II 7 III)	183 (63 I 81 II 39 III)
28% (60% I 30% II 10% III)	72% (34% I 43% II 23% III)
II + III 19% III 15%	II + III 81% III 85%
I + II 31% I 41%	I + II 69% I 59%

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The tumors appear not so early as in the case of the English. The tumor age is similar to No. 8.

III. Tumor Age.

In discussing the various strains of mice, we have already had occasion to mention the age at which the tumors appeared. We did not, however, express the frequency of tumors of a certain strain in relation to the number of mice alive at a certain period. This is done in the following pages. Here those strains which have a sufficient number of mice for the purpose of such a calculation are divided into three classes according to their age. We include here furthermore strains which were not mentioned previously. In each case we state how many mice were alive in each of the three periods and what percentage of the mice alive had tumors at that period of life. Thus we come to a more accurate determination of the frequency of tumors at a certain period of life and we can decide whether the various strains have the same tumor age and whether this tumor age is correlated with other factors. The figures which we thus obtain are only an approximation to the real conditions; they are not absolutely correct, because in computing the figures we ignored the fact that during the various periods mice died at different times, while we assumed for the purpose of obtaining a relatively small number of comparable figures in each strain, that they lived to the end of that period of life. However, we believe that this inaccuracy does not interfere seriously with a representation of the actual facts.

In defining the tumor age of the various strains we had further to consider the fact that the figures obtained stating the per cent of tumor mice living at a certain period depended also on the absolute frequency of tumors of a certain strain and not only on the distribution of tumors according to the age of the animals. In order to eliminate the former factor it was necessary to determine in all strains the relation between the percentage of tumor mice in each of the three periods of life.

On the following pages we state in each strain the number of tumor mice expressed in per cent of living mice in each period.

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We then state the frequency of tumors in the strain as a whole, and then follows the relation between tumor rate in the first and second plus the third periods, and the relation between tumor rate in the first and the second periods, between tumor rate in the second and third, and lastly between the tumor rates in the first plus the second and third periods of life. Thus we obtain an insight into the relative frequency of tumors in the three different periods of life.

European + No. 10 (Nov. 3d strain).

I	Period	254	mice	63	tumors	= 25%	72% I : II+III = 1 : 7 I : II = 1 : 3
II	"	148	"	120	"	= 81%	II : III = 1 : 1 I+II : III = 1.2 : 1
III	"	46	"	39	"	= 88%	

English A.

I	Period	175	mice	52	tumors	= 29%	63% I : II+III = 1 : 4 I : II = 1 : 2.2
II	"	80	"	51	"	= 64%	II : III = 1.3 : 1 I+II : III = 1.9 : 1
III	"	16	"	8	"	= 50%	

English Sable.

I	Period	252	mice	115	tumors	= 46%	70% I : II+III = 1 : 2.8 I : II = 1 : 1.5
II	"	88	"	61	"	= 69%	II : III = 1 : 1 I+II : III = 1.9 : 1
III	"	21	"	13	"	= 62%	

English except Silver. Total:

I	Period	537	mice	219	tumors	= 41%	68% I : II+III = 1 : 3.2 I : II = 1 : 1.7
II	"	203	"	146	"	= 72%	II : III = 1.3 : 1 I+II : III = 2 : 1
III	"	38	"	22	"	= 58%	

English Silver.

I	Period	117	mice	8	tumors	= 6.1%	7% I : II+III = 1.2 : 1 I : II = 1.2 : 1
II	"	69	"	4	"	= 5.1%	
III	"	16	"	0	"	= 0 %	

No. 8.

I	Period	268	mice	24	tumors	= 8%	30% I : II+III = 1 : 9.3 I : II = 1 : 4.7
II	"	150	"	57	"	= 38%	II : III = 1 : 1 I+II : III = 1.2 : 1
III	"	73	"	27	"	= 37%	

No. 8½.

I	Period	158	mice	6	tumors	= 4%	17% I : II+III = 1 : 6.2 I : II = 1 : 3.7
II	"	109	"	17	"	= 15%	II : III = 1.5 : 1 I+II : III = 1.9 : 1
III	"	40	"	4	"	= 10%	

Carter.

I	Period	67	mice	12	tumors	= 17 %	39% I : II+III = 1 : 3 I : II = 1 : 1.3
II	"	40	"	9	"	= 22.5%	II : III = 1 : 1.2 I+II : III = 1.4 : 1
III	"	17	"	5	"	= 28 %	

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German.

I	Period	20	mice	3	tumors	= 15%	50% I : II+III = 1 : 7.4 I : II = 1 : 3
II	"	11	"	5	"	= 45%	II : III = 1 : 1.5 I+II : III = 1 : 1.1
III	"	3	"	2	"	= 66%	

European.

I	Period	94	mice	5	tumors	= 5%	16% I : II+III = 1 : 4.2 I : II = 1 : 2.2
II	"	62	"	7	"	= 11%	II : III = 1.1 : 1 I+II : III = 1.6 : 1
III	"	28	"	3	"	= 10%	

Heitler.

I	Period	102	mice	4	tumors	= 4%	27% I : II+III = 1 : 10.7 I : II = 1 : 10.7
II	"	56	"	24	"	= 43%	II : III ∞ I+II : III ∞
III	"	14	"	0	"	= 0%	

London.

I	Period	120	mice	9	tumors	= 7%	27% I : II+III = 1 : 6.6 I : II = 1 : 2.7
II	"	75	"	14	"	= 19%	II : III = 1 : 1.4 I+II : III = 1 : 1
III	"	36	"	10	"	= 27%	

European + No. 10 (Nov. 8 strain).

I	Period	96	mice	20	tumors	= 21%	65% I : II+III = 1 : 6.1 I : II = 1 : 2.6
II	"	61	"	33	"	= 54%	II : III = 1 : 1.4 I+II : III = 1 : 1
III	"	12	"	9	"	= 75%	

Cream + 10.

I	Period	174	mice	4	tumors	= 3%	36% I : II+III = 1 : 17 I : II = 1 : 5
II	"	152	"	23	"	= 15%	II : III = 1 : 2.4 I+II : III = 1 : 2
III	"	96	"	35	"	= 36%	

No. 8 + German.

I	Period	244	mice	21	tumors	= 9%	41% I : II+III = 1 : 6.8 I : II = 1 : 3.1
II	"	183	"	51	"	= 28%	II : III = 1 : 1.2 I+II : III = 1 : 1.1
III	"	86	"	28	"	= 33%	

101 + 103.

I	Period	152	mice	6	tumors	= 4%	34% I : II+III = 1 : 17 I : II = 1 : 7.2
II	"	97	"	27	"	= 29%	II : III = 1 : 1.4 I+II : III = 1 : 1.2
III	"	45	"	18	"	= 40%	

German + Carter.

I	Period	358	mice	4	tumors	= 1%	9% I : II+III = 1 : 14 I : II = 1 : 4
II	"	275	"	11	"	= 4%	II : III = 1 : 2.5 I+II : III = 1 : 2
III	"	176	"	17	"	= 10%	

European Hybrid + 8½ F_4.

I	Period	473	mice	8	tumors	= 2%	16% I : II+III = 1 : 13 I : II = 1 : 2.5
II	"	364	"	19	"	= 5%	II : III = 1 : 4.2 I+II : III = 1 : 3
III	"	233	"	50	"	= 21%	

Silver + 10.

I	Period	234	mice	26	tumors	= 11%	36% I : II+III = 1 : 5.2 I : II = 1 : 1.6
II	"	154	"	29	"	= 18%	II : III = 1 : 2.2 I+II : III = 1 : 1.4
III	"	75	"	29	"	= 39%	

(103 + European) F_1 + III. Daughter of No. 10.

I	Period	168	mice	3	tumors	= 2%	17% I : II+III = 1 : 15 I : II = 1 : 4.5
II	"	115	"	11	"	= 9%	II : III = 1 : 2.2 I+II : III = 1 : 3
III	"	67	"	14	"	= 21%	

European 151 + 8 F_5

I	Period	125	mice	8	tumors	= 6%	30% I : II+III = 1 : 7 I : II = 1 : 3.8
II	"	86	"	20	"	= 23%	II : III = 1.2 : 1 I+II : III = 1.5 : 1
III	"	47	"	9	"	= 19%	

European + 102, 103.

I	Period	146	mice	2	tumors	= 1.5%	21% I : II+III = 1 : 22 I : II = 1 : 5.3
II	"	109	"	9	"	= 8 %	II : III = 1 : 3.1 I+II : III = 1 : 2.6
III	"	76	"	19	"	= 25 %	

London + (European + 103) F_3.

I	Period	78	mice	0	tumors	= 0%	5% II : III = 1 : 2
II	"	66	"	2	"	= 3%	
III	"	33	"	2	"	= 6%	

Cream.

I	Period	177	mice	0	tumors	= 0%	2.3% II : III = 1 : 2
II	"	120	"	2	"	= 2%	
III	"	53	"	2	"	= 4%	

8½ + English Sable.

I	Period	48	mice	20	tumors	= 41%	61% I : II+III = 1 : 1.5 I : II = 1 : 1.5
II	"	15	"	9	"	= 60%	
III	"	1	"	0	"	= 0%	

8½ + No. 10 F_1 (Nov. 8 strain).

I	Period	82	mice	6	tumors	= 7%	49% I : II+III = 1 : 10 I : II = 1 : 4
II	"	68	"	19	"	= 27%	II : III = 1 : 1.6 I+II : III = 1 : 1.3
III	"	35	"	15	"	= 43%	

(8½ + No. 10) + No. 10 (Nov. 8).

I	Period	72	mice	5	tumors	= 7%	36% I : II+III = 1 : 11 I : II = 1 : 2.7
II	"	48	"	9	"	= 19%	II : III = 1 : 3.2 I+II : III = 1 : 2.3
III	"	20	"	12	"	= 60%	

Michigan Wild + 101 F_2.

I	Period	50	mice	13	tumors	= 26%	58% I : II+III = 1 : 4 I : II = 1 : 1.5
II	"	23	"	9	"	= 39%	II : III = 1 : 1.8 I+II : III = 1 : 1.1
III	"	10	"	7	"	= 70%	

121 (English Tan) + Cream.

I	Period	92	mice	16	tumors	= 7%	42% I : II+III = 1 : 8.8 I : II = 1 : 4.4
II	"	56	"	18	"	= 31%	II : III = 1 : 1 I+II : III = 1.2 : 1
III	"	16	"	5	"	= 31%	

European + 146 (English Tan).

I	Period	74	mice	3	tumors	= 4%	28% I : II+III = 1 : 11 I : II = 1 : 5.5
II	"	58	"	13	"	= 22%	II : III = 1 : 1 I+II : III = 1.1 : 1
III	"	22	"	5	"	= 23%	

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English 121 + German.

I	Period	39	mice	10	tumors	= 25%	49% I : II+III=1 : 3.6 I : II=1 : 1.6
II	"	18	"	7	"	= 39%	II : III=1 : 1.3 I+II : III=1.3 : 1
III	"	4	"	2	"	= 50%	

White English + (8 + German) F_4.

I	Period	82	mice	27	tumors	= 33%	63% I : II+III=1 : 2.2
II	"	33	"	25	"	= 73%	
III	"	1	"	0	"	= 0%	

We may arrange the various strains into four classes according to the relative frequency of tumors in the various periods of life. While there are some slight variations within each class, on the whole the various strains in each class behave in a similar manner.

Class I. Early Tumors.

I : II + III = 1 : 2.8 I : II = 1 : 1.6 II : III = 1 : 1.2 I + II : III = 1.5 : 1

English 68%.
English Silver 7%.
8½ + English Sable 61%.
English (121) + German 49%.
White English + (8 + German) F_4 63%.
Michigan Wild + 101 F_2 (in Period III, more tumors) 58%.
Carter 39%.
European 16%.

Average tumor rate 45%.

Class II. Tumors of Medium Age.

I : II + III = 1 : 7.4 I : II = 1 : 3.5 II : III = 1 : 1.2 I + II : III = 1.2 : 1.

Nov. 3 strain 72%.
Nov. 8 strain 65%.
No. 8 30%.
No. 8½ 17%.
Heitler (in II period very high tumor rate) 27%.
London 27%.
European + 146 (English Tan), (not quite as good, in Period I, less tumors) 28%.
No. 8 + German 41%.
Silver + 10 (less tumors in Period III, more in II, nearer Class I) 36%.
European Hybrids 151 + 8 F_5 (Period I low, Period II high, Period III lower, somewhat better than Class II) 30%.
121 + Cream 42%.
German 50%.

Average tumor rate 38%.

Class III. Great Frequency of Tumors in Period III.

I : II + III = 1 : 10.5 I : II = 1 : 3.3 II : III = 1 : 2.4 I + II : III = 1 : 1.8.

8½ + No. 10 F_1 (Nov. 8 strain) 49%.
(8½ + No. 10) + No. 10 (Nov. 8 strain) (in Period III many tumors) 36%.

Average tumor rate 42½%.

Class IV. Late Tumors.

I : II + III = 1 : 16.3 I : II = 1 : 4.7 II : III = 1 : 2.6 I + II : III = 1 : 2.3.

Cream + 10 36%.
Cream 2.3%.
101 + 103 = [101 + (103 + European)] 34%.
German + Carter 9%.
European Hybrid + 8½ F_4 = [(European + 102) + 8½ F_4] 16%.
Hybrids (103 + European) F_1 + III, daughter of No. 10 17%.
European + 102, 103 21%.
London + (European + 103) F_3 5%.

Average tumor rate 17.5%.

In Class I, in which the tumors appear relatively early, we find in the combined second and third periods of life 2.8 times as many tumors as in the first period; in the second period of life 1.6 times as many tumors as in the first period; in the third period 1.2 times as many tumors as in the second period; and in the combined first and second periods 1.5 times as many tumors as in the third period. While, therefore, in this class the tumors are more frequent in the second period than in the first, and in the third than in the second, the differences in the percentages are not very marked. The tumors appear here relatively early, the percentage of tumors in the first period of life being considerable. We include in this group eight strains, counting the various English substrains as one strain, with the exception of the Silver. We added to the name of each strain the number giving the frequency of tumor mice in per cent of the total number of mice, irrespective of the age at which they appear. If we designate as a high tumor rate 40 to 100 per cent, as a medium tumor rate 20 to 40 per cent, and as a low tumor rate 0 to 20 per cent, we find that five of the eight strains have a high tumor rate, one a medium tumor rate (with a figure near the lower border of the high tumor rate), and two a low tumor rate. Of these two, one

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strain (Silver) is related to the other English strain, which has a high tumor rate. We see therefore that the tumor age can vary independently of the tumor frequency. English Silver has like the other English strain an early tumor age, but in contradistinction to the other English mice a very low tumor rate. The average tumor rate in Class I is 45 per cent. It would be higher if we had counted the various English strains separately.

In Class II the tumors in the second period are 3.5 times more frequent than in the first period; the tumors in the second period are therefore here relatively (compared to the frequency in the first period) considerably more frequent than in the first class. In the third period the tumors are 1.2 times more frequent than in the second period; this is the same proportion between the frequency in the third and second periods as in the first class; but absolutely the tumors are here more frequent in the third period; 11 strains belong to this class; 4 of these have a high, 6 a medium, and 1 a low tumor rate. The average tumor rate is 38 per cent.

Class III consists of only two strains, which as far as the relation between the number of tumors in the first and second period of life is concerned, stand between the first and second class, but are nearer the second class, in which, however, the relative frequency of tumors in the third period is greater than in the second class. The average tumor rate is here 42.5 per cent.

Class IV contains the late tumors. The relative preponderance of the frequency of tumors in the second over that in the first period is here greater than in the first, second, or third class, and again the preponderance of the third period over the second period is greater than in the former classes. Eight strains are included in this class. None of these show a high tumor rate, 2 show a medium, and 6 a low tumor rate. The average tumor rate in this class is 17.5 per cent.

We may draw from this analysis the following conclusions:

1. There exists a certain relationship between tumor frequency and tumor age. On the whole, the more frequent the tumors, the earlier they appear in the various strains. It might be conceivable that the frequency of the tumors was independent of the tumor age;

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that in strains in which the tumor frequency is greater, the tumors appear in the same percentage in the various periods of life, but this is evidently not the case. In strains in which the tumor frequency is greater, they appear on the whole also at an earlier period of life.

2. This parallelism between tumor frequency and tumor age is, however, not complete. The tumor age seems to be as characteristic for a strain as the tumor rate. In strains with a similar rate of frequency, the tumor age may be different. This difference is probably not accidental, because (1) if we have substrains related to each other, the tumor age is usually similar in all of them, and (2) the tumor age of the constituent strains seems to influence the tumor age of the crosses. How far this latter relation holds good, we shall discuss in another communication. On the other hand, we found in the case of the substrain Silver that it had a similar tumor age to the English strain, although the tumor rate of the Silver is considerably lower than that of the other English strains.

3. The tumor age is transmitted from generation to generation in a similar manner to the tumor rate. We may therefore conclude that in all probability tumor rate and tumor age represent distinct unit factors which frequently, but not in all cases, are in some way linked to each other.

4. We may furthermore conclude that the age where the maximum of tumors occurs varies in different strains. While in some it appears in the second period of life, in others it is in the third period. Here again the maximum is on the whole reached at an earlier period of life in strains with a high tumor rate. But here also peculiarities exist in different strains.

SUMMARY.

1. It is possible to split a strain of mice into certain substrains in which the tumor incidence is in some way linked to the color of the mice. Thus we could split off from the English strain, which as a whole and in various substrains with mixed colors (English A and Sable) has a high tumor rate, substrains with light tan color and pink eyes (101 and Tan) which have a high tumor rate like the large majority of the English mice, and two other apparently

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recessive strains breeding true, which have a very low tumor incidence (Silver and Silver Fawn). Therefore, certain combinations of factors which determine certain colors of mice determine at the same time the tumor incidence of these strains or substrains. In the majority of cases isolated families bred through several generations separately from the majority of the other substrains give approximately the same tumor rates as the others; in some cases, however, it may perhaps be possible to separate from the main strain a family with a different rate.

2. The tumor incidence and the tumor age found in the earlier periods of our work are approximately the same as in the more recent period. On the whole, the results obtained in successive generations of the same strain also agree well with each other; the results are fairly constant; the deviations which occur are in most cases due to the small number of animals observed in the certain generations. Discarding all the mice dying in the first or in the first and second periods of life usually does not alter essentially the tumor ratio of a certain strain.

3. A certain relationship exists between tumor frequency and tumor age. On the whole, the more frequent the tumors, the earlier they appear in the various strains. This parallelism between tumor frequency and tumor age is, however, not complete. The tumor age seems to be as characteristic for a certain strain as the tumor rate. Certain substrains which differ in tumor frequency may show approximately the same tumor age. Strains with similar tumor frequency may show a different tumor age. We may therefore conclude that in all probability tumor rate and tumor age represent distinct unit factors, which are frequently, but not in all cases, linked in some manner to each other.

4. The age at which the maximum of tumors appears varies in different strains. The maximum may fall into the second or third period of life. On the whole, the maximum is reached at an earlier period of life in those strains which have a high tumor rate. But here also peculiarities exist in different strains.