# STUDIES ON THE RELATION BETWEEN TUMOR SUSCEPTIBILITY AND HEREDITY. I.

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(Received for publication, October 15, 1923.)

## INTRODUCTION.

The failure of the many attempts to demonstrate a parasitic origin for neoplastic disease in mammals has shifted attention to other possible factors in its etiology. One of these is the relation between tumor growth and heredity. Although mammals offer rather poor material for research in genetics on account of the small number of offspring produced, the demonstration of the histological and biological similarity of the neoplasms of man and rodents has led to the selection of the latter for experimentation.

Studying the inoculated tumor in mice, Tyzzer and Little[1] and Little[2] investigated the inheritance of conditions permitting the growth of an implant and have obtained results which are compatible with an explanation on the basis of multiple factors. The study of the spontaneous tumor as a close parallel to the condition found in man, has attracted a series of investigators. An early communication by Thorel[3] simply reported the occurrence of a high tumor rate observed in a stock

[1] Little, C. C., and Tyzzer, E. E., Further experimental studies on the inheritance of susceptibility to a transplantable tumor, Carcinoma (J. w. A.) of the Japanese waltzing mouse, *J. Med. Research*, 1915–16, xxxiii, 393; Studies in the inheritance of susceptibility to a transplantable sarcoma (J.w.B) of the Japanese waltzing mouse, *J. Cancer Research*, 1916, i, 387.

[2] Little, C. C., The heredity of susceptibility to a transplantable sarcoma (J.w.B.) of the Japanese waltzing mouse, *Science*, 1920, li, 467; Factors influencing the growth of a transplantable tumor in mice, *J. Exp. Zool.*, 1920, xxxi, 307.

[3] Thorel, C., Kasuistisches zum Kapitel der sog. Mäusecarcinome, *Verhandl. deutsch. path. Ges.*, 1908, xii, 59.

of laboratory mice. Tyzzer[4] from his observations upon mice with cancerous ancestry (mainly primary lung tumor) concluded that heredity plays a part in cancer incidence. Murray[5] from a biometrical treatment of groups of mice with mammary gland tumor in which he compared females from mothers or grandmothers which had cancer to those with more remote cancerous ancestry, reached the same conclusion. Slye[6] and Loeb and Lathrop[7] have raised strains of mice showing an extraordinarily high cancer incidence, and Loeb has maintained groups with high and low rates at fairly constant percentages for a number of generations. Slye states that she has raised four strains from three to five generations without cancer. The ages of the individuals are not given. These facts and certain crosses that have been made, have been interpreted as meaning that hereditary units traveling in the germ plasm of the different strains, persistently express themselves in the constitutions of the individuals of each succeeding generation.

Little and his collaborators[8] in a resumé of data upon human beings, collected by the Eugenics Record Office at Cold Spring Harbor, makes a comparison of the cancer incidence among persons having a cancerous parent, to the incidence in the population at large, and finds that the disease is much more frequent among individuals of cancerous parentage than would be expected according to the law of probability. In statistics upon cancer incidence among human beings some allowance must be made for uncertainties in diagnosis.

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[4] Tyzzer, E. E., A study of heredity in relation to the development of tumors in mice, *J. Med. Research*, 1907–08, xvii, 199; A series of spontaneous tumors in mice with observations on the influence of heredity on the frequency of their occurrence, Fifth Report of the Cancer Commission of Harvard University, Boston, 1909, 153.

[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] Slye, M., The incidence and inheritability of spontaneous cancer in mice. Preliminary report, *Z. Krebsforsch.*, 1913, xiii, 500; Second report, *J. Med. Research*, 1914, xxx, 281; Third report, *J. Med. Research*, 1915, xxxii, 159; Fifth report, *J. Cancer Research*, 1916, i, 479; Seventh report, *J. Cancer Research*, 1916, i, 503; Ninth report, *J. Cancer Research*, 1917, ii, 213; Thirteenth report, *J. Cancer Research*, 1920, v, 53; Sixteenth report, *J. Cancer Research*, 1921, vi, 139; Eighteenth report, *J. Cancer Research*, 1922, vii, 107.

[7] Lathrop, A. E. C., and Loeb, L., Further investigations on the origin of tumors in mice. I. Tumor incidence and tumor age in various strains of mice, *J. Exp. Med.*, 1915, xxii, 646; II. Tumor incidence and tumor age in hybrids, *J. Exp. Med.*, 1915, xxii, 713; IV. The tumor incidence in later generations of strains with observed tumor rate, *J. Cancer Research*, 1919, iv, 137; V. The tumor rate in hybrid strains, *J. Exp. Med.*, 1918, xxviii, 475.

[8] Inheritance of a tendency to "Cancer" in man, *Carnegie Institution of Washington, Year Book No. 20*, 1921, 139.

It was with the aim of securing Mendelian data that we planned a series of crosses involving the hybridization of different strains of mice. Unfortunately several epidemics of so called mouse typhoid ravaged the major portion of the older groups. From the fragment that remained, the data, while as yet incomplete, have furnished some facts sufficiently interesting to warrant a preliminary presentation of the subject at this time.

Much of the confusion which has characterized the discussion of the inheritability of a tendency to cancer, has arisen from a certain vagueness connected with the connotation of "heredity." In recent years, the confirmation and elaboration of the Mendelian law has not only clarified our conception of heredity, but furnishes definite tests which may be applied practically, at least in the case of the lower animals. The essential characteristic of Mendelism, *i.e.* segregation of the hereditary units in the germ cells, can be clearly seen in the offspring from hybrids of known ancestry. Therefore, the breeding test to be applied consists of making up hybrids and then analyzing what has occurred by inbreeding or backcrossing. To investigate any particular character, an individual possessing it is crossed with one that does not have it, and whose ancestors were free from it. The offspring from such a cross are usually all alike in either having or not having the character. If it appears in the first filial generation it is termed dominant, if not, it is called recessive. The following diagram may serve to illustrate these facts.

$P_1$ $\quad \frac{D}{D} \times \frac{R}{R}$

Germ cells D, D R, R.

$F_1$ $\quad \frac{D}{R} \quad \frac{D}{R}$

Germ cells D, R D, R.

$F_2$ $\quad \frac{D}{D} \quad \frac{D}{R} \quad \frac{R}{D} \quad \frac{R}{R}$

Since the germ cell is duplex in nature, the dominant and recessive parents are represented by the formulæ $\frac{D}{D}$ and $\frac{R}{R}$, respectively. These individuals can produce egg or sperm of but one kind (either D or R). Fertilization of one by the other results in individuals $\frac{D}{R}$ which by definition look like the parent with the dominant character, although they carry the recessive gene also. This generation produces germ cells of two kinds, D and R, so that random fertilization gives four combinations, three of which are individuals showing the dominant character, and one is

recessive. Of the dominant, however, two carry the recessive latent gene and are termed heterozygous.

If the $F_1$ generation, instead of being inbred, is backcrossed to either type of parent, a different ratio is obtained in the $F_2$.

| | | | |
|---|---|---|---|
| $F_1$ | $\frac{D}{R}$ | × | $\frac{D}{D}$ (Parent). |
| Germ cells | D, R | | D, D |
| Backcross | $\frac{D}{D}$ $\frac{D}{R}$ | | $\frac{D}{R}$ $\frac{D}{D}$ |

As illustrated above, if the backcross is made to the parent with the dominant character, the resulting offspring are all of the dominant type, a higher percentage than in the second filial generation from the first cross and equal to that of the first filial generation. If the backcross is made to the recessive parent, half of the progeny will be dominant (heterozygous) and half recessive—giving a smaller percentage of dominants than when the $F_1$ is inbred.

These ratios are obtained when a character is dependent on one gene in the germ cell. If two genes are concerned the parents may be represented by the formulæ $\frac{DA}{DA}$ (dominant) and $\frac{RB}{RB}$ (recessive). Their offspring will be heterozygous $\left(\frac{DA}{RB}\right)$ dominants capable of producing four types of germ cells, DA, DB, RA, RB. If there is no linkage the four kinds will be produced in equal numbers.

| | | | | | |
|---|---|---|---|---|---|
| P | $\frac{D}{D}\frac{A}{A}$ | | × | | $\frac{R}{R}\frac{B}{B}$ |
| $F_1$ | $\frac{D}{R}\frac{A}{B}$ | | | | |
| Germ cells | DA | DB | RA | RB | |
| $F_2$ | $\frac{D}{D}\frac{A}{A}$ | $\frac{D}{D}\frac{B}{A}$ | $\frac{R}{D}\frac{A}{A}$ | $\frac{R}{D}\frac{B}{A}$ | |
| | $\frac{D}{D}\frac{A}{B}$ | $\frac{D}{D}\frac{B}{B}$ | $\frac{R}{D}\frac{A}{B}$ | $\frac{R}{D}\frac{B}{B}$ | |
| | $\frac{D}{R}\frac{A}{A}$ | $\frac{D}{R}\frac{B}{A}$ | $\frac{R}{R}\frac{A}{A}$ | $\frac{R}{R}\frac{B}{A}$ | |
| | $\frac{D}{R}\frac{A}{B}$ | $\frac{D}{R}\frac{B}{B}$ | $\frac{R}{R}\frac{A}{B}$ | $\frac{R}{R}\frac{B}{B}$ | |

With random fertilization there will be sixteen classes of offspring of the second filial generation. Every class which contains at least one "dose" of both D and A

will produce the dominant type. There are nine dominants to seven recessives. But the backcross to the homozygous dominant parent will give a larger and to the recessive parent a smaller proportion of animals showing the dominant character.

$F_1$ $\frac{DA}{RB} \times \frac{DA}{DA}$ (Parent).

Backcross $\frac{DA}{RB}$ (dominant), $\frac{DA}{DA}$ (dominant), $\frac{DA}{DB}$ (dominant), $\frac{DA}{RA}$ (dominant).

Likewise when the character depends on three or four more genes, different ratios will be obtained in the $F_2$, but the backcross to the dominant and recessive types will yield larger and smaller numbers of dominants, respectively, than obtained from the inbred $F_1$. These ratios, therefore, constitute a check upon the data, and may be used as controls in an experiment.

It is possible that tumor susceptibility is not inherited according to the simple schemes outlined above. Morgan has suggested that it might be due to a somatic mutation. In that case, while still Mendelian, more complicated relationships would be indicated. It is not necessary to discuss these further possibilities until the simpler explanations have been tested.

### *The Tumor.*

The work more especially of Slye, has indicated that tumors of particular types or particular organs are inherited as separate units. Slye found that a number of neoplasms of one type can be concentrated in one (or a few) strains of mice, while other strains may be free from them. In the present paper one type only will be considered—that which is reported to be the most common among mice, namely the mammary gland tumor. It usually presents itself as an adenocarcinoma, or carcinoma. No attempt has been made to subdivide further these growths, and classify them as different units. Autopsies are made upon all mice that die, and all tumors are verified from the microscopic examination of sections.

When the character dealt with is a neoplasm, certain complications are introduced into the situation. (1) In the stocks under observation adenocarcinoma has appeared only in the female sex. Slye has reported sarcoma and carcinoma of the mammary gland as occurring in the male, but it is not common, and in the strains used in these

experiments neither sarcoma nor carcinoma has been found in the mammæ of the male mouse. (2) Variability. Susceptibility to neoplastic disease, in mice as in human beings, is characteristic of middle or old age. While a cancer *may* appear in a mouse as young as $4\frac{1}{2}$ months, the average tumor age in many races is $1\frac{1}{2}$ years, and sometimes the disease does not make its appearance until the individual is 2 or 3 years old. At 2 years a female mouse has passed the reproductive period and is considered old. Many mice may live to the comparatively advanced age of 2 years and die without producing a tumor, which, had they lived a few months longer might have been classed as tumor mice. The fact that a mouse dies without showing a tumor does not necessarily mean that it was incapable of producing one. Tumor incidence in any strain is probably always higher than statistics would indicate. From these facts it is readily seen that tumor susceptibility must be regarded genetically as a variable character. (3) Breeding. Mice with tumors are difficult to breed, not only on account of their age, but often their poor health seems to prevent reproduction. In practice the young adults for breeding are selected from strains of high tumor incidence on the chance that the individuals so chosen will eventually develop tumors.

## EXPERIMENTAL.

At the time these experiments were commenced, we were in possession neither of a strain very rich in tumor mice, nor one which was known to be tumor free, but at the same time that we were endeavoring to build up such races, a tentative beginning was made on the problem by outcrossing strains from different sources.

In all cases, the female parents were taken from the tumor stocks which had been acquired by purchase from the Lathrop Mouse Farm. These strains had been under observation for some time, and though none showed a very high tumor incidence, individuals were chosen from those giving the highest rate and also, as far as possible, from mothers which had developed tumors. For the male parents various stains were used. One was obtained through the courtesy of Dr. C. C. Little from the Carnegie Institute at Cold Spring Harbor. While it was not guaranteed as a non-tumor stock, it had been in Dr. Little's possession for 7 years; fairly large numbers had been raised, some of the females attaining old age, and no external tumors had ever been found. Males were used also from the pink eyed, brown spotted race which had been under observation by Dr. Detlefsen at

the University of Illinois, for 4 years, without any tumors having been observed. The strain of albinos procured from Dr. Bagg at the Cancer Memorial Hospital is known to have produced a few mice with mammary gland cancer, but the incidence is probably low. (It is still under observation.) Five agouti males caught at Bronx Park were used on the supposition that they were wild. One of them, however, when mated with albinos, gives albinos in the $F_1$, suggesting that its ancestry may include an escape from the laboratory and that it is not wild. The two caught at Staten Island and in New York City are probably really wild stock.

TABLE I.

Fifteen crosses between females from high tumor strains and males from outside sources. In the third column opposite each male is listed the number of his daughters which had not developed tumors at 10 months of age (or later) and in the fourth column the number of his daughters which did have tumors.

| Catalogue No. of male. | Source of male parent. | No. of daughters without tumor. | No. of daughters with tumor. |
|---|---|---|---|
| 15-47 | Little. | 8 | 4 |
| 16-45 | " | 8 | 3 |
| 16-46 | " | 4 | 3 |
| 16-04 | Detlefsen. | 10 | 5 |
| 15-69 | " | 3 | 0 |
| 15-71 | " | 0 | 1 |
| 15-97 | " | 1 | 0 |
| 17-82 | Bagg. | 2* | 1 |
| 17-76 | " | 5* | 1 |
| 17-92 | " | 0* | 2 |
| 18-97 | " | 2* | 7 |
| 18-37 | Bronx. | 0* | 1 |
| 18-64 | " | 2* | 1 |
| 18-63 | Staten Island. | 0* | 1 |
| 19-83 | New York. | 0* | 1 |

* Many daughters still living.

The results of the crosses are given in Table I. Many losses occurred in all generations, not only from the usual causes incident to mouse culture, but also from the series of typhoid epidemics. In certain cases, whole groups were wiped out, including parents and offspring. If the latter had not reached tumor age, the entire group is not reported. Also certain experiments begun somewhat later than the rest, in which the $F_1$ are just reaching tumor age, are not given here. With these exceptions, Table I includes *all* outcrosses which have been

made, giving all females in the $F_1$ which reached the age of 10 months or more.

It is to be noted that one or more of the daughters developed tumors in every cross here listed, with two exceptions. In one of these cases Male 15-97 had but one daughter which lived to be as old as 10 months, in the other, Male 15-69, there were but three females. If a tendency to cancer is hereditary the immediate appearance of tumors in the $F_1$ indicates either that tumor susceptibility is dominant or that none of the males used as parents were non-tumor mice. If tumor susceptibility is dominant, a female which develops a tumor may have the formula of either $\frac{D}{D}$ (homozygous) or $\frac{D}{R}$ (heterozygous), but it is impossible to tell by inspection to which type she belongs. If she

TABLE II.

The distribution of tumors among the daughters of tumor mice obtained from the stock room.

| Catalogue No. of the mouse. | Non-tumor daughters. | Tumor daughters. |
|---|---|---|
| H5 | 5 | 2 |
| H8 | 3 | 1 |
| H11 | 2 | 0 |
| H13 | 1 | 0 |
| H15 | 0 | 1 |

were $\frac{D}{D}$ all her daughters should inherit tumor susceptibility, if $\frac{D}{R}$, half of them would receive it, but since the character is, in addition, variable, even that 50 per cent might not actually develop neoplasms. Therefore, the two exceptions cited above, in which one and three daughters did not show tumors, are not adequate tests for dominance and may be disregarded. As for the other case, the chances are enormously against finding 100 per cent tumor mice in a random selection of thirteen males from six different sources.

It will be interesting to compare these data with another group of individuals which have come under observation. From time to time, females with tumors have been brought to us from the mouse breeding station of The Rockefeller Institute. Five of these

were pregnant when brought in. In the stock from which they came the old females are continually discarded, so that the average age is below tumor age, and the tumor rate is not known. It is possible that they had mated with tumor mice. Nevertheless it is of interest that three of them had tumor mice among their daughters and the other two had too small a number of offspring (two and one females, respectively), to be regarded as contradictory evidence. An examination of the daughters of tumor mice in our own inbred supply stock, does not reveal any conflicting data. Usually only a small number of daughters lived to tumor age. Heterozygosity of the mother and the variability of the character would necessitate a fairly large number of daughters to form a decisive test. In the one instance in which eleven females lived more than 12 months, only one had a tumor, which suggests that the degree of variability is great or that more than one gene is involved.

From the first seven crosses given in Table I, the majority (though not all) of the descendents have reached tumor age. Unfortunately, both of the stocks (Little and Detlefsen) from which the male parents were taken were lost before giving sufficient data to prove that they were non-tumor stocks (or individuals), but the $F_1$ as well as having been inbred were backcrossed with the tumor stock. If tumor susceptibility is hereditary and dominant, a higher percentage of tumor mice should appear from the backcrossed than from the inbred parents, and a comparison of the two rates should function as a control for the experiment. A summary of the data from these two generations, as well as from the $F_1$, and the female parents used for both the original and backcrossed mothers is given in Table III.

The females selected for the original cross showed a slightly smaller percentage of tumors (7 out of 26) than did the backcross mothers, where about one-third (19 out of 56) proved to be tumor mice. As before stated, however, many of those which did not succumb to neoplasms may genetically have been tumor mice—even homozygous, without developing a tumor. In the $F_2$, 12 mice out of 89 (a 1:6.5 ratio) had tumors, and the backcross daughters gave 50 tumors in a total of 159 mice (about 1:2). thus fulfilling the expectation. If we note only those offspring of which the mothers (original mothers and backcross mothers) were tumor mice we find for the $F_2$, 6 tumors in

30 mice (1:4) and for the backcross 13 tumors in 39 mice a (1:2 ratio). Here again the backcross gives more tumors than the inbred generation. The backcross ratio equalled the $F_1$, which showed 16 tumor mice in 50 (1:2). Since the male parents have not been proven non-tumor individuals the $F_2$ ratio of 1:6.5 cannot be used as a basis for calcu-

TABLE III.

Results of experiments in each of which one male was crossed with several females from tumor stock and his sons backcrossed to females from tumor stock. The lists show how many daughters ($F_1$), granddaughters ($F_2$), and daughters from the backcross did or did not have tumors.

| Catalogue No. of male parent. | No. of female parents (P) without and with tumor. | | No. of daughters ($F_1$) without and with tumor. | | No. of granddaughters ($F_2$) without and with tumor. | | Backcross mothers. | | No. of daughters from backcross without and with tumor. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Without. | With. | Without. | With. | Without. | With. | Without. | With. | Without. | With. |
| 15-47 | 3 | 4 | 8 | 4 | 53 | 5 | 23 | 11 | 69 | 24 |
| 16-04 | 7 | 0 | 10 | 5 | 13 | 3 | 7 | 1 | 13 | 6 |
| 16-46 | 1 | 2 | 4 | 3 | 5 | 4 | 7 | 6 | 25 | 20 |
| 15-69 | 1 | 1 | 3 | 0 | 0 | 0 | 0 | 1 | 2 | 0 |
| 15-71 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15-97 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 16-45 | 5 | 0 | 8 | 3 | 5 | 0 | 0 | 0 | 0 | 0 |
| | 19 | 7 | 34 | 16 | 77 | 12 | 37 | 19 | 109 | 50 |

TABLE IV.

The distribution of tumor mice among $F_2$ and backcross females classified according to whether or not they have been bred.

| | Not bred. | | Bred. | |
|---|---|---|---|---|
| | Non-tumor. | Tumor. | Non-tumor. | Tumor. |
| $F_2$ | 9 | 1 | 19 | 2 |
| Backcross | 15 | 5 | 20 | 10 |

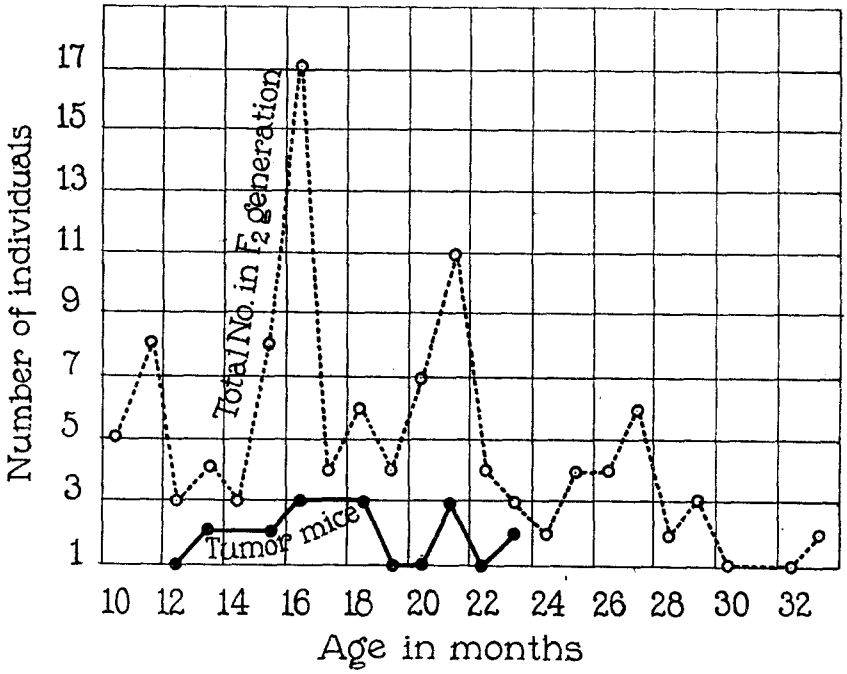
lating the number of genes responsible for the character. The comparison of the $F_2$ and backcross is, however, valid evidence for the inheritability of cancer susceptibility, but the figures should probably be modified by a consideration of the environmental factor of irritation.

The word "susceptibility" as applied to the inheritance of tumor growths, doubtless connotes in the minds of many investigators the tendency on the part of animal tissue to respond by producing abnormal growths when subjected to various stimuli, known or unknown (chemical, mechanical, etc.). This was suggested by the prevalence of certain types of neoplasms among classes of people such as paraffin workers, chimney sweeps, betel-nut chewers who are accustomed to localized chronic irritation, and the experimental work done upon the artificial production of tumors by means of parasites, coal tar, etc., has emphasized the importance of this aspect of the situation. In the case of cancer of the mammæ in mice, breeding and rearing young has been regarded as the contributory factor. It is not an absolutely necessary one since mice which have never had young do produce tumors, but Lathrop and Loeb[9] have published percentages indicating that in non-breeding mice the tumor rate was, on the whole, somewhat lower and the tumor age higher than in breeding mice. The amount of decrease varied in different strains. In only one strain was the tumor rate higher in the non-breeding than in breeding mice; in the other eight strains tested it was lowered, sometimes slightly, sometimes to a considerable extent. There is a little evidence in our stocks which seems corroborative, but the point is being further investigated. In the data here presented there are two small classes of bred and non-bred mice. Among the non-bred, in the $F_2$ there was 1 tumor mouse to 9 without tumors, as against 5 tumor mice to 15 without tumor in the backcross.

In the group which was bred there were 2 tumor mice and 19 without tumors in the $F_2$, compared with 10 tumors to 20 without in the backcross. The method of recording the production of young, which had been satisfactory for small groups of mice, unfortunately proved unreliable for large groups, so that there is a doubtful class in both $F_2$ and backcross mice. Among the $F_2$ in the doubtful group, there were

[9] Lathrop, A. E. C., and Loeb, L., The influence of pregnancies on the incidence of cancer in mice, *Proc. Soc. Exp. Biol. and Med.*, 1913, xi, 38; Further investigations on the origin of tumors in mice. III. On the part played by internal secretion in the spontaneous development of tumors, *J. Cancer Research*, 1916, i, 1. Loeb, L., VI. Internal secretion as a factor in the origin of tumors, *J. Med. Research*, 1919, xl, 477.

9 tumors to 49 non-tumors. If we classify these individuals in a manner least favorable to the theory (a manifestly unfair procedure) and regard all the tumor mice as having been bred and the non-tumors as not having been reproduced, there would be 11 tumors to 19 non-tumors in the $F_2$ group that was bred, compared with 10 to 20 in the backcross; and in the non-bred group 1 tumor to 58 non-tumor $F_2$ mice against 5 tumor to 15 non-tumor in the backcross. In all these



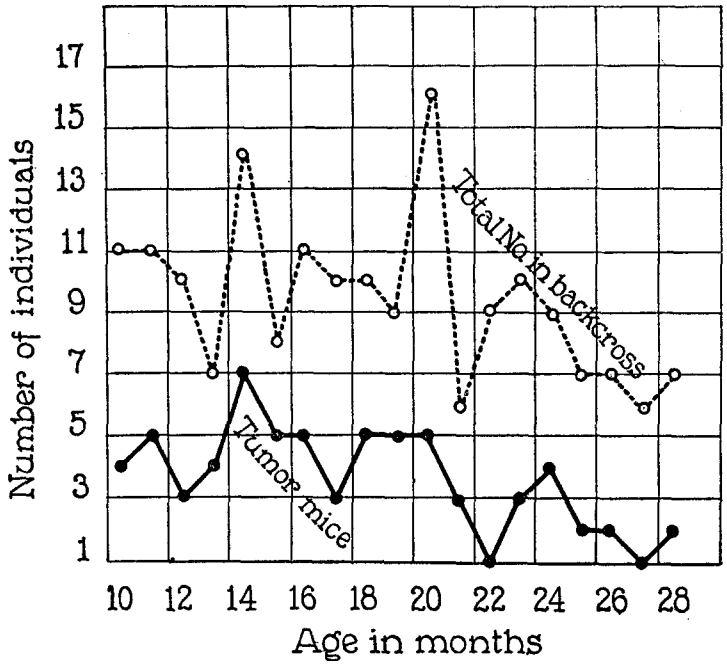

TEXT-FIG. 1. The age distribution of the $F_2$ individuals.

comparisons the greater number of tumors in the backcross as compared with the $F_2$ supports the theory that tumor susceptibility is inherited.

In any discussion of cancer rate, age distribution is a matter of importance, the conclusion reached above, however, cannot be discredited on the ground that the various groups were not comparable as to age. From Text-figs. 1 and 2 it will be seen that the ages cover much the same range. In the experiment as a whole, tumors appeared

at a lower age in the backcross than in the $F_2$. The comparison of the bred and non-bred groups appears equally valid considered from the point of view of age distribution as illustrated in Text-fig. 3.

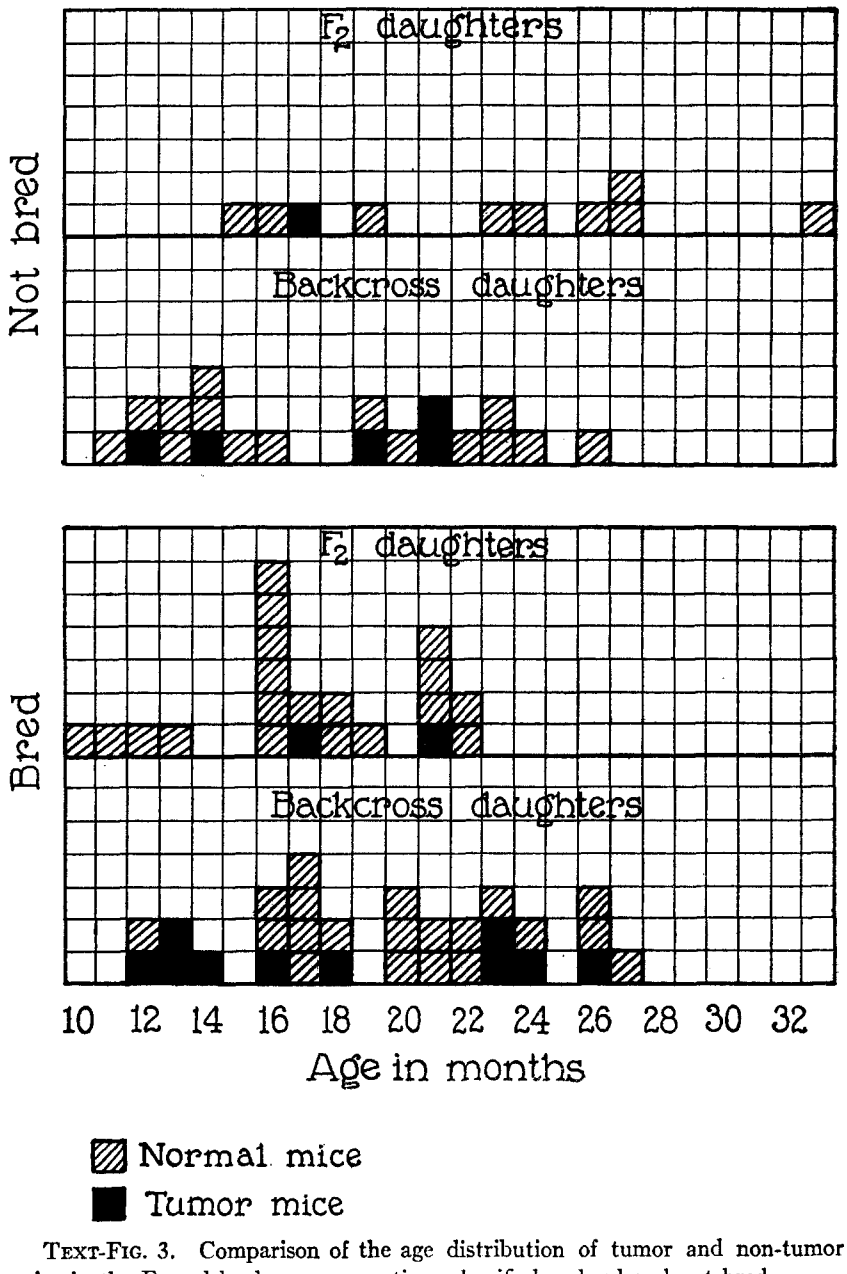
It may be pointed out that the evidence for dominance presented here is not in accord with the findings of some authors. Slye, especially, has held to the view that "cancer behaves as a recessive."[10] In the present report attention is directed to tumors of the mammary




TEXT-FIG. 2. The age distribution of the backcross individuals.

gland only, not to cancer in general. It is true that a character apparently uniform wherever it occurs, may in reality comprise several different entities and be caused by separate genes in the germ cell. For example, in chickens, there are four different kinds of whites, three of which are recessive and one is dominant. It is possible that mammary carcinoma also may act as a dominant in one race and as a recessive in another. The data given in the pedigrees published by

[10] Slye,[6] Eighteenth report, p. 76.




TEXT-FIG. 3. Comparison of the age distribution of tumor and non-tumor mice in the $F_2$ and backcross generations classified as bred and not bred.

Slye[6] includes 130 females with tumors of the mammary gland and the daughters obtained from them by either inbreeding or outcrossing to other (tumor?) stocks. Of these, 102 females had daughters with mammary gland tumor, while 28 females had daughters without such tumors. Of the 28 without cancerous daughters, the majority (24) had only 1 or 2 female offspring, but 1 mother had 3 daughters, 2 mothers had 4 daughters, and 1 had 5 daughters without cancer. There are apparently but two cases in which cancer stock has been crossed with absolutely non-cancer stock. In Strain 84, one cancerous female outcrossed to a male from non-tumor stock had one daughter and son without cancer. Slye calls this Branch II. This suggests the existence of additional offspring which were not reported. In Strain 164 a daughter of a cancerous mouse was outcrossed to a male from non-cancer stock and produced 4 sons and 4 daughters without tumor. Only individuals at least 6 months old (as we understand), are included in these charts, but the exact ages are not given, and since the average tumor age is much higher than 6 months and since the number of individuals reported is meager, these pedigrees do not present conclusive data. Possibly there are additional data not reported by Slye or incorrectly interpreted by us but the evidence, as published, seems inadequate to support the theory of recessiveness as applied to the mammary gland tumor.

## CONCLUSION.

In this preliminary report there are presented some of the results obtained from crossing mice from tumor strains with males from other sources. The comparison of the tumor incidence in the inbred and backcross daughters, though the numbers given are small, supports the theory that the tendency to develop neoplasms is hereditary and the frequency with which tumors appear in the first filial generation of such crosses, indicates that the character is dominant.

Additional experiments involving larger numbers are in progress.