THE INCIDENCE AND INHERITABILITY OF SPONTANEOUS TUMORS IN MICE.*

(*Second Report.*†)

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The solution of the question as to whether or not cancer is inheritable has its chief value in the light it will throw upon the nature of cancer, and consequently upon the nature of the cure for cancer and the methods of preventing the increase of this disease in the race. For if cancer should prove to be inheritable in the strict sense, as an Albinic coat is inheritable, this fact must guide all future search for anything in the nature of its prevention or its cure.

It is with this point of view and handling cancer as a unit character, definitely to be proved transmissible or non-transmissible, that I have conducted my experiments. I have used exactly the same methods which one would use in testing the inheritability of any stock Mendelian character, and have judged the results by the same criteria used in judging the inheritability, for example, of Albinism. If the results when fully tabulated shall show that cancer can be handled as a unit character and can be transmitted as such — put in where it has not occurred before and drawn out as an extracted strain — it will finally answer the objection that even if transmitted the basis for such transmission might be intra-uterine infection or germ-cell contamination.

This work is the outcome of four years' previous work on general problems of heredity carried on at the University of

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† The first report of this work appeared in Zeitschrift fur Krebsforschung, Dreizehnter Band, Drittes Heft., 1913, the report of a paper delivered in May, 1913, before the American Society for Cancer Research.

Chicago, during which time I accumulated a stock of some five thousand mice of known ancestry. This pedigreed stock, in which spontaneous tumors arose, has furnished the entire material for these experiments in cancer.

I have dealt with spontaneous tumors only; no grafts of any nature have been made; for the question of the inheritability of cancer can no more be solved with grafted tumors than any other problem of inheritability is to be solved by the use of an acquired character.

For this reason no attempt has been made to find strains of mice immune to grafts of tumors. (For the methods of elimination of contagion as a factor in the transmission of cancer see first report.)

I wish to reëmphasize here the difficulties in the way of definitely testing the inheritability of cancer:

Cancer does not appear early and the mice are swept off by infections, accidents, etc., before they are old enough to show whether or not they would have cancer, so that I believe any results will always show considerably fewer cancers than are potential in the strain. Out of the three hundred and ninety cases of tumors reported here, only one occurred in a mouse under six months old, so that in setting six months as the lower range of cancer age, we are establishing a very conservative limit.

It must be remembered further that many mice pass through the first year or more of life and then develop cancer. It is therefore not certain of any mouse that dies under a year old whether it might not have developed cancer later. Indeed, I have in my laboratory mice over four years old. It is possible they may even yet develop cancer, although if they had died at any previous age they would have been classed as non-cancerous.

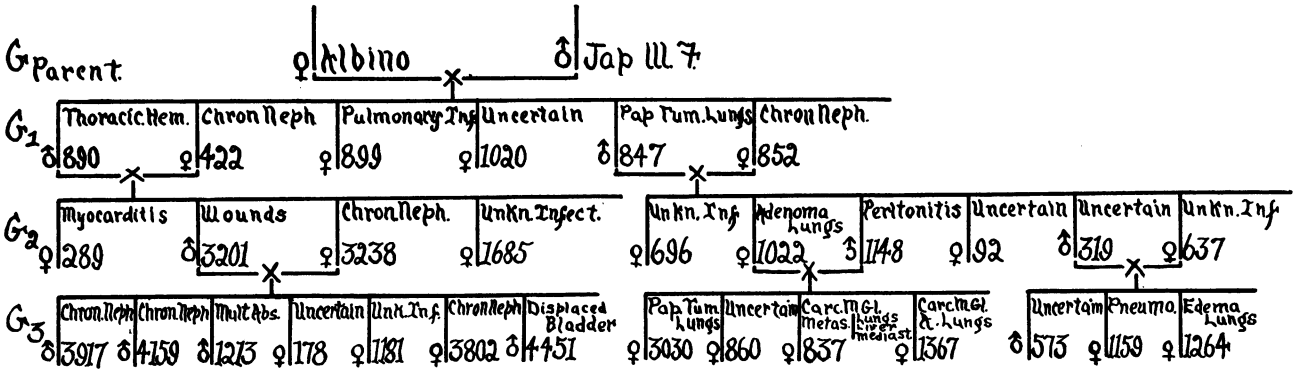
Again, the fact that cancer is likely to appear sporadically in any strain is a complicating factor not met with in testing such characters as color. For example, there are only one or two recorded cases of cancer in house mice, yet (omitting one strain, No. 186, previously reported) I had one example

in the first two hundred autopsies on house mice, viz., a desmoid sarcoma of the mammary gland in a male. This does not necessarily mean a percentage of one cancer in every two hundred house mice. It may prove to be one in a thousand.

Among my Peromyscus Californicus and Novoboriensis (two species of the wild "Whitefoot") there was one case in the first fifty, viz., a squamous-cell carcinoma of the mouth in a female; and in the second fifty a carcinoma of the mammary gland in a female. These two mice belonged not only to different strains but to different species, though both were species from California.

Out of the mass of material which has accumulated I have selected some additional typical cases for presentation here.

Strain 264


G Parent
♀ Albino × ♂ Jap III. 7.
G1
♂ 890 × ♀ 422 ♀ 899 ♀ 1020 ♂ 847 × ♀ 852
Thoracic Hem. | Chron Neph | Pulmonary Inf | Uncertain | Pap Tum. Lungs | Chron Neph.
G2
♀ 289 ♂ 3201 × ♀ 3238 ♀ 1685 ♀ 696 ♀ 1022 × ♂ 1148 ♀ 92 ♂ 319 × ♀ 637
Myocarditis | Wounds | Chron Neph. | Unkn. Infect. | Unkn. Inf | Adenoma Lungs | Peritonitis | Uncertain | Uncertain | Unkn. Inf
G3
♂ 3917 ♂ 4159 ♂ 1213 ♀ 178 ♀ 1181 ♀ 3802 ♂ 4451 ♀ 3030 ♀ 860 ♀ 837 ♀ 1367 ♂ 573 ♀ 1159 ♀ 1264
Chron. Neph | Chron. Neph | Mult. Abs. | Uncertain | Unk. Inf. | Chron Neph | Displaced Bladder | Pap Tum Lungs | Uncertain | Carc. M.Gl. Metas. Lungs Liver Mediast. | Carc. M.Gl. & Lungs | Uncertain | Pneumo. | Edema Lungs

Strain 264. — Hybrid strain between Albino female and Japanese Whitefoot male.

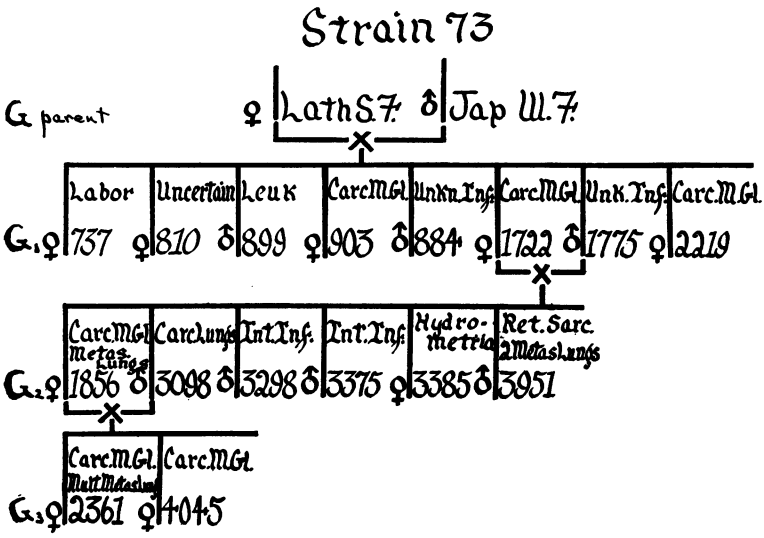
Both parents died before autopsies began. It is impossible to tell whether they might have had cancer.

Of their six offspring, Male No. 847 died of papillary tumor of the lungs.

In the first generation the mating of Female No. 422 with Male No. 890, neither of which had cancer, gave four offspring no one of which had cancer; neither did cancer appear in the third generation in this branch of the strain.

The mating of first generation Female No. 852 with Male No. 847, papillary tumor of the lungs, produced one tumor among their six offspring, viz.: Female No. 1022, adenoma of the lungs. In the third generation of this branch of the family in which Female No. 1022 was the mother, there appeared three cases of tumor.

This strain shows about sixteen per cent of tumors.



Strain 73. — A portion of this chart appeared previously. It is here extended to include later members of the strain. Hybrid strain between a silver faun female and a Japanese Whitefoot male.

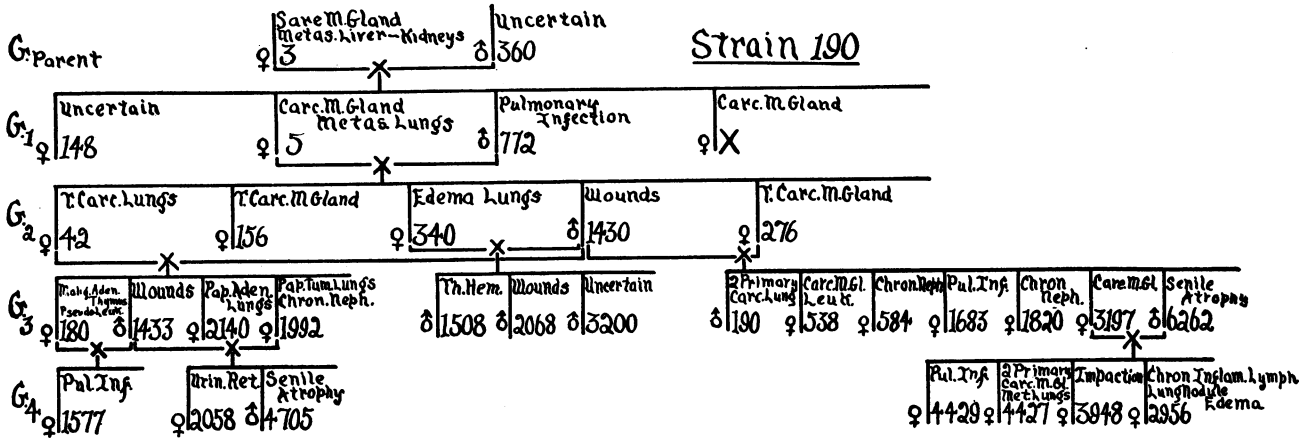
Both parents came of cancer families but both died before autopsies were held, and it is uncertain whether or not they would have developed cancer.

Among their offspring there were three cases of carcinoma, one of leukemia, one died early in labor, and three died early of infections.

Two of their offspring, Female No. 1722 and Male No. 1775, mated, produced six young, two of which died of carcinoma, one of retroperitoneal sarcoma, two of intestinal infection, and one of hydrometria.

In the second generation, the mating of Female No. 1856 with Male No. 3098, both with carcinoma, gave two females, both of which died of carcinoma.

This strain shows about forty-four per cent of tumors.


Strain 190
G. Parent
♀ 3 Sarc. M. Gland Metas. Liver—Kidneys
♂ 360 Uncertain
G. 1
♀ 148 Uncertain
♀ 5 Carc. M. Gland Metas. Lungs
♂ 772 Pulmonary Infection
♀ X Carc. M. Gland
G. 2
♀ 42 T. Carc. Lungs
♀ 156 T. Carc. M. Gland
♀ 340 Edema Lungs
♂ 1430 Wounds
♀ 276 T. Carc. M. Gland
G. 3
♀ 180 Mal. Adeno. Thymus Pseudol. Leuk.
♂ 1433 Wounds
♀ 2140 Pap. Adeno. Lungs
♀ 1992 Pap. Tum. Lungs Chron. Neph.
♂ 1508 Th. Hem.
♂ 2068 Wounds
♂ 3200 Uncertain
♂ 190 2 Primary Carc. Lung
♀ 538 Carc. M. Gl. Leuk.
♀ 584 Chron. Neph.
♀ 1683 Pul. Inf.
♀ 1820 Chron. Neph.
♀ 3197 Carc. M. Gl.
♂ 6262 Senile Atrophy
G. 4
♀ 1577 Pul. Inf.
♀ 2058 Urin. Ret.
♂ 4705 Senile Atrophy
♀ 4429 Pul. Inf.
♀ 4427 2 Primary Carc. M. Gl. Met. Lungs
♀ 3948 Impaction
♀ 2956 Chron. Inflam. Lymph. Lung Nodule Edema

Strain 190. — Hybrid cross between a Japanese Whitefoot female and an Albino male.

The parent, Female No. 3, had sarcoma of the mammary gland with metastases in liver and kidney. The male died of uncertain cause.

Of their four young, two had carcinoma of the mammary gland.

Female No. 5, with cancer, mated with Male No. 772, pulmonary infection, had five young, three of which died of carcinoma.

In the second generation the mating of Female No. 42, carcinoma of the lungs, with Male No. 1430, who died of wounds, gave in the third generation two cases of tumor of the lungs, Female No. 180, with malignant adenoma of the thymus and pseudo-leukemia, and Male No. 1433, who died of wounds. The mating of Female No. 180 with Male No. 1433 gave only one offspring, that died early of pulmonary infection.

The mating of Female No. 1992, with tumor of the lungs, with Male No. 1433 (wounds), gave only two offspring, Female No. 2058, who died early of urinary retention, and Male No. 4705, who died of senile atrophy without cancer.

Again, in the second generation, the mating of Female No. 340, edema of the lungs, with Male No. 1430 (death by wounds) gave no cancer in the third generation.

In the third branch of the second generation of this strain the mating of this same male, No. 1430, with Female No. 276, carcinoma of the mammary gland, gave in the third generation three cases of carcinoma and four cases without cancer.

The mating of Female No. 3197, cancerous, with Male No. 6262, who died of senile atrophy without cancer, gave in the fourth generation of this branch of the strain: Female No. 4429, pulmonary infection; Female No. 4427 with two primary carcinomas of the mammary glands and metastases in the lungs; Female No. 3948, who died of fecal impaction; and Female No. 2956, killed by edema of the lungs and showing at autopsy a lung nodule not yet definitely tumor, with chronic inflammation of lymphoid tissue.

In this strain nearly fifty per cent of cancer is shown.

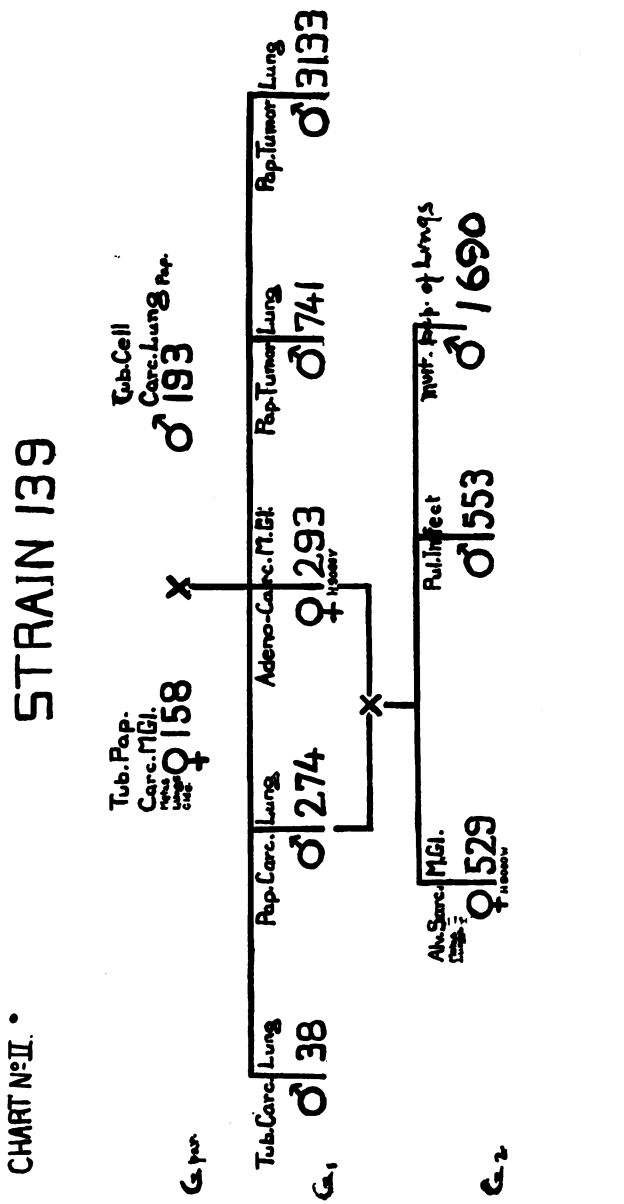


CHART No II.
STRAIN 139
Tub. Pap. Carc. Mgl. ♀158
Tub. Cell Carc. Lung Pap. ♂193
Tub. Carc. Lung ♂38
Pap. Carc. Lung ♂274
Adeno-Carc. M.Gl. ♀293
Pap. Tumor Lung ♂741
Pap. Tumor Lung ♂3133
Alv. Sarc. M.Gl. ♀529
Pul. Infect ♂553
Inf. Pap. of Lungs ♂1690
G1
G2

Strain 139. — Albino mice (inbred for over twenty-five generations).

Parents, female and male, both had cancer. Every one of the young still living at the time my autopsies began had tumors either benign or malignant.

Of their young the two which produced young, Female No. 293 and Male No. 274, both had cancer. This pair had three offspring: Female No. 529 with sarcoma of the mammary gland; Male No. 553, who died young of pulmonary infection, and Male No. 1690, multiple papillomas of the lungs.

Strain 146. — A hybrid strain of Albinos.

The parent, Female No. 529, is shown in Chart II., Strain 139, a strain closely inbred for many generations. Both grandparents and both parents had cancer. She herself had cancer. The parent male in the cross, Male No. 242, was an Albino derived from reds. The red strain had cancer and the derived Albino strain had cancer. Whether or not this male would have developed cancer is uncertain.

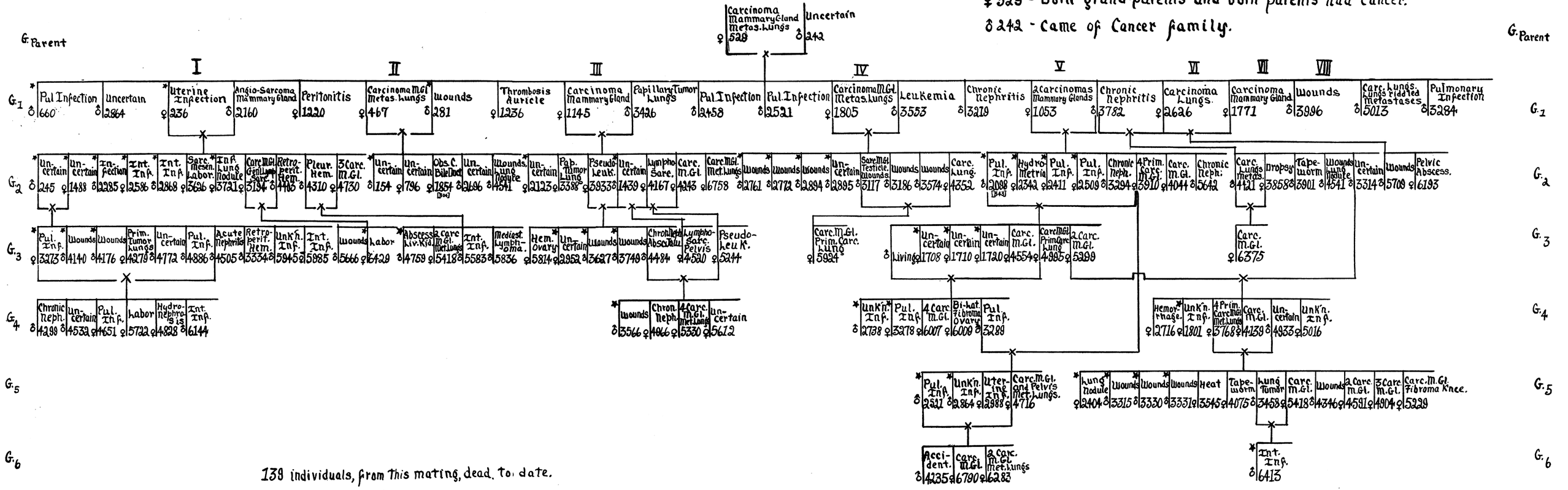
Of their offspring twenty-two have died and are shown in this chart as generation I. Three died before cancer age. Of the remaining nineteen, nine had tumors, only one of which was not malignant at the time of death, Male No. 3426. One died of leukemia, Male No. 3553.

Strain 146

A hybrid Strain of Albinos.

♀529 - Both grand-parents and both parents had Cancer.

♂242 - Came of Cancer family.



139 individuals, from this mating, dead to date.

42 died before Cancer age.

42 unquestioned cases of Tumor, nearly all malignant.

3 Lung Nodules, not yet definitely tumor.

3 cases of Leukemia and Pseudo-Leukemia.

The strain shows nearly 43% of Cancer.

✱ Died before Cancer Age.

In this first generation seven matings were made:

I.

Female No. 236, uterine infection, with Male No. 2160, angio-sarcoma of mammary gland. Of their eleven young, six died early of infections. Of the remaining five, Female No. 3194 had carcinoma of the mammary gland with general lympho-sarcomatosis.

Female No. 3626, mesenteric sarcoma; Male No. 4310, pleural hemorrhage; Male No. 4403, retroperitoneal hemorrhage, and Female No. 4730, three carcinomas of the mammary gland.

In this second generation three matings were made:

(*a.*) Female No. 1488 with Male No. 245, both of whom died early of unknown causes.

Of the ten offspring from this cross, one primary tumor of the lung appeared in the third generation; so far no tumors have appeared in the fourth.

(*b.*) Again, in this second generation, Female No. 3194, carcinoma of the mammary gland, was mated with Male No. 4403, retroperitoneal hemorrhage. Of their two offspring which have died, neither had tumor.

(*c.*) Again, in this same second generation, Female No. 4730, three carcinomas of the mammary gland, was mated with Male No. 4310, pleural hemorrhage.

Of their four offspring which are dead to date, two had cancer; Female No. 5418, two carcinomas of the mammary gland, metastases in the lungs, and Male No. 5836, mediastinal lymphoma.

II.

The second mating in the first generation was Female No. 467, carcinoma of the mammary gland, metastases in the lungs, with Male No. 281, who died of wounds.

Of their four young, one died of wounds but had a lung nodule not yet malignant. The others died of uncertain causes.

III.

The third mating in this first generation was Female No. 1145, carcinoma of the mammary gland, with Male No. 3426, papilloma of the lungs.

Of their seven offspring dead to date, two died before cancer age. Of the remaining five —

Female No. 3388, died of papilloma of lungs; Female No. 3933, of pseudo-leukemia; Female No. 4167, lympho-sarcoma of the entire subcutaneous tissue; Female No. 4243, carcinoma of the mammary gland; Female No. 6758, carcinoma of the mammary gland.

(*a.*) In the second generation Female No. 3933, pseudo-leukemia, was mated with Male No. 1439, cause of death uncertain. Of their five young —

Female No. 5814 died of ovarian hemorrhage. Female No. 2952 died before cancer age.

The three males died of wounds received in fighting; two of them died immediately of their wounds; the third, Male No. 4484, died later of chronic nephritis following trauma and an abscess of the jaw at the point of an old wound.

(*b.*) Again, in this second generation, Female No. 4167, lympho-sarcoma, was mated with male No. 1439, cause of death uncertain. Their one offspring which has died, Female No. 4520, had lympho-sarcoma of the pelvis.

(*c.*) Again, in this second generation, Female No. 4243, carcinoma of the mammary gland, was mated with the same Male No. 1439, uncertain. Their one offspring dead to date, Female No. 5244, had pseudo-leukemia. This female, No. 5244, mated with a third generation male from crossing II., Male No. 4484, with chronic nephritis, had four offspring dead to date, of which Female No. 5330 had four carcinomas of the mammary gland, metastases in the lungs.

IV.

The fourth mating in the original first generation was Female No. 1805, carcinoma of the mammary gland, metastases in the lungs, with Male No. 3553, leukemia. Of their

eight young, six males died of wounds, all but one before cancer age.

Male No. 3117 was picked up wounded from fighting and rushed to the hospital badly wounded. He lived, but developed at wounded points a spindle-cell sarcoma of the mammary gland and a spindle-cell sarcoma of the testicle.

The remaining offspring, Female No. 4352, died of carcinoma of the lung.

(*a.*) This female, No. 4352, with carcinoma of the lung, was mated with Male No. 3117, who died of two spindle-cell sarcomas. Their one offspring dead to date, Female No. 5924, had carcinoma of the mammary gland and primary carcinoma of the lung.

V.

The fifth mating in the original first generation was Female No. 1053, two carcinomas of the mammary gland, with Male No. 3782, chronic nephritis.

Of their eight offspring, four died before cancer age; of the remaining four, two males, Nos. 3294 and 5642, died of chronic nephritis. Female No. 3910, four primary carcinomas of the mammary gland, and Female No. 4044, carcinoma of the mammary gland.

(*a.*) In this second generation, Female No. 3910, carcinoma of the mammary gland, was mated with Male No. 2098, pulmonary infection. Of their offspring three died before cancer age. Female No. 4554, Female No. 4995, and Female No. 5299 had carcinoma of the mammary gland.

In the third generation, Female No. 4995, carcinoma of the mammary gland, primary carcinoma of the lungs, mated with a male still living, have five offspring dead to date, two that died before cancer age, and Male No. 3289, pulmonary infection, Female No. 6007, four carcinomas of the mammary gland, and Female No. 6009, bilateral ovarian fibromas.

(*a.*) One of these males, Male No. 3289, pulmonary infection, mated with Female No. 3910 of the second generation, four carcinomas of the mammary gland, gave four

young dead to date: two males that died before cancer age; Female No. 2988, uterine infection, and Female No. 4716, carcinoma of the mammary gland and carcinoma of the pelvis with metastases in the lungs.

(*b.*) Female No. 4716 mated with Male No. 2521 gave three young dead to date, viz.:

Male No. 4235, accidentally killed; Female No. 6790, carcinoma of the mammary gland; Female No. 6283, two carcinomas of the mammary gland, metastases in the lungs.

VI.

In the sixth mating of the original first generation, Female No. 2626, carcinoma of the lungs with metastases in the lymph glands and chest wall, was mated with Male No. 3782, chronic nephritis. Of their five offspring, two males had tumors, viz.: Male No. 4421, carcinoma of the lungs with metastases; Male No. 4541, died of wounds but showed at autopsy a lung nodule not yet malignant.

(*a.*) In this second generation, Male No. 4421, carcinoma of the lung with lung metastases, was mated with Female No. 3858, dropsy. Of their young there is dead to date only Female No. 6375, who died of carcinoma of the mammary gland.

(*b.*) Again, in this second generation, Male No. 3314 (cause of death uncertain) was mated with Female No. 5299, third generation in the fifth mating, who had two carcinomas of the mammary gland.

Of their six young, Female No. 3768 and Female No. 4139 had cancer.

In this fourth generation, Female No. 3768, four carcinomas of the mammary gland, lungs riddled with metastases, was mated with Male No. 4933, the cause of whose death was uncertain. Of their twelve young, four died before cancer age. Of the remaining eight, five died of tumor, all but one being malignant.

VII.

Of the seventh mating in the original first generation, Female No. 1771, carcinoma of the mammary gland with Male No. 3782, chronic nephritis, two offspring only are dead to date: Male No. 5709, wounds; Female No. 6193, pelvic abscess.

SUMMARY OF CHART V.

Of the one hundred and thirty-nine individuals sprung from the mating of Female No. 529 and Male No. 242, there are forty-two unquestioned cases of tumor, nearly all malignant; three lung nodules not yet definitely tumor; three cases of leukemia and pseudo-leukemia; forty-two died before cancer age.

It is noticeable that the crossing of second generation Female No. 3933, pseudo-leukemia, and Male No. 1439, uncertain, produced Male No. 4484, chronic nephritis, which when mated with Female No. 5244, third generation, pseudo-leukemia, gave Female No. 5330 with four carcinomas of the mammary gland.

DISCUSSION.

All of my observations seem to indicate that cancer is a mode of growth. Let me compare briefly the results of these charts with the results of one infection somewhat frequent among mice, viz., sarcosporidiosis.

Where mice are allowed to stay in the same cage, every mouse at autopsy shows some degree of sarcosporidiosis, whereas members of the family kept elsewhere are no more liable to it than any other strain of mice. But among members of cancer strains, cancer crops out no matter where the mice are kept. A daughter frequently develops cancer before the mother does, and months after they have been separated. A granddaughter will develop cancer who was not born until after the death of the tumorous grandparent.

My work so far has covered over six thousand five hundred autopsies, among which there are three hundred and

ninety cases of unquestioned tumor. The numbers alone are illuminating as showing the results obtained in deliberate breeding for cancer.

There are many cases of multiple carcinoma, particularly in the mammary gland; also a great number of cases of lung metastases, from microscopic nodules to lungs riddled with them. A very interesting point in this connection is the series which might be made of these proliferative processes. In the mammary gland series there are nodules not malignant, borderline cases, and the true malignant carcinomas and sarcomas. Such cases occur also in the liver tumors and in the mediastinal tumors. But especially in the lung series one finds the finest possible gradation from inflammatory nodules, through nodules becoming malignant, to the most malignant infiltrating cancers. (This will be the subject of a paper soon to appear.) Often two or more of these stages occur in the same mouse. These series of different stages of proliferation are very significant. In the non-tumor strains they generally remain mere inflammatory proliferation. In the tumor strains they are likely to go on into malignant neoplasms unless the subject dies of some other cause too early for full development of the cancer to occur.

As further evidence of cancer as a mode of growth, another general observation might be of interest. This is based upon over six thousand five hundred autopsies.

In the four general death periods the main causes of death are as follows:

I.	Infancy	Malnutrition. Not a fair start in life. Infection from the mother.
II.	Adolescence	Infections, largely pulmonary.
III.	Prime of reproductive life	Wounds among males (from fighting). Labor, or slight infection during pregnancy among females. Infections, largely concerned with reproduction; heart disease, dropsy, nephritis, cancer.

IV.	Later life	Senile atrophy. Chronic Bright's disease. Obesity; with chronic nephritis or heart disease. Cancer.

In infancy and adolescence, the normal growth periods, no cancer occurs, though this is the age of infections, particularly of pulmonary infections; whereas the lung tumors rarely occur under one year of age and frequently not until after the second year.

In the prime of reproductive life, much cancer is found where it is hereditary, usually at the point of overstrain.

In the later period — the period of practically no infections — an almost equal number of cancers occur among mated and unmated mice. In the mated they usually appear at the point of lesion from overstrain; in the unmated possibly because there is no normal growth using the excess products of metabolism.

In connection with the occurrence of cancer at the point of overstrain, it is interesting to note that probably ninety-five per cent of the mammary gland cancers in reproductive females occur at the anterior and posterior glands. These are the mammæ most used. A mouse in suckling her young does not lie on her side like a cat or a dog, but hovers over the young with the arms raised. The anterior and the posterior mammæ are in this way much more exposed than those lying intermediate.

I have had two very interesting cases of the slowing up of cancer growth during a highly reproductive period. Female No. 5417, tumor first observed October twenty-fourth, 1912. After the external appearance of the tumor she had five litters of young, and during all this time the progress of her tumor was very slow. The last litter was born May tenth, 1913, and the young were suckled by her for three weeks, when they were removed. After this her cancer grew to enormous size and with great rapidity, and she died August thirty-first, 1913.

The other is the case of a mouse still living. Her tumor appeared externally August twenty-sixth, 1913. She has

had three litters of young since then and is still bearing. At this time, over six months since its appearance, the tumor is still of very moderate growth. Whereas, females which have no young after cancer appears rarely live over two months, frequently less than one. The bearing and rearing of young have in these two cases been accompanied by a notable retardation of cancerous growth.

It is quite the contrary with infections among mice. A very slight touch of an infection will carry off a pregnant female, where an advanced stage is necessary to kill an unpregnant female or a male.

I have said that cancer is a mode of growth — a mode of growth probably allied to regenerative processes and probably possible to any individual at the point of overstrain and in certain conditions. For example, the application of the X-ray probably will produce human cancer in any individual. Cancer is probably possible in any mouse, but it is likely to occur where heredity predetermines.

All mice are subjected to the same conditions in my laboratory, both external and in the strain of living. All mother mice suckle their young; cancer develops in those whose heredity determines it. Lesions in the lung are likely to occur in any mouse from any one of many possible causes. Heredity determines in which cases it shall develop into malignant cancer. (Within a few months I expect to have ready for publication a much more complete report of these and other experiments in cancer.)

[I wish to express my thanks to Dr. H. Gideon Wells and to Miss Harriet Holmes for their assistance in diagnosis.]