equality of correlation exists, and whether the somatic resemblance can be used as a test for predicting the consequences of inbreeding, are points which must be left for future elucidation.

(v) Some of the limitations of the method of this paper have been pointed out, and others are obvious. The extension to the case where more than one pair of allelomorphs is considered might conceivably be valuable when more data have been collected, and should not prove difficult.

In particular, a method which assumes the absence of selective mating and ignores the existence of differential fertility can claim no finality. It is hoped, however, that some of the conclusions are fairly exact deductions from the simple Mendelian theory as it stands at the present time.

In conclusion, I wish to thank Prof. Pearson for the help noted in the paper, and for much stimulating criticism.

Cancerous Ancestry and the Incidence of Cancer in Mice.

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The purpose of these experiments has been the collection of data sufficiently abundant and accurate to determine whether an enhanced liability to cancer is transmitted in the case of mice from parents to offspring. In a preliminary note in 1909* a short account was given of the manner in which these experiments have been conducted.

The animals have all been housed and fed in a uniform manner in one room. They have been kept in large cages, which have been cleaned regularly, and the environment has been as uniform as it has been possible to make it. During the past five years nearly 1600 animals have been bred, the two sexes contributing approximately equal numbers. Of them, 562 females which have lived for six months or more form the materials of the present paper. The incidence of the disease is so dependent on the age and sex of the animals that, in order to get comparable groups, only mice of the same sex and of approximately the same age may be reckoned together.

* E. F. Bashford and J. A. Murray, "The Incidence of Cancer of the Mamma in Female Mice of Known Age," 'Roy. Soc. Proc.,' 1909, B, vol. 81, p. 310.

They have been arranged in age-periods of three months' duration, this being the shortest interval which gives reasonably large figures in each group.

From the pathological standpoint the data are practically perfect. All the animals which did not present a tumour during life were carefully examined for tumours after death, and it is scarcely possible that any growth of considerable size has escaped being examined microscopically and recorded. The mice in which tumours were discovered during life have been kept under observation till death. The tumours have been examined microscopically in every case, and only those which were undoubtedly malignant are reckoned in the tables and ancestries.

The figures refer to females only. The number of cases of malignant new growths in males bred in the laboratory is so small that a statistical study of their frequency could not give useful results, nor do the males which developed new growths appear in the ancestry of the females at present under consideration.

The tables show the ratio which deaths from cancer, and more especially cancer of the mamma, bear to deaths from all causes at each of seven three-monthly age-periods for female mice over a number of years. The age-period in which mice dying of diseases other than cancer are entered is given by the age at death. The mice which have died of cancer are entered in the age-period embracing their ages at the time the existence of a tumour was discovered, and not in that embracing their age at death.* This basis for the age groups has been chosen instead of the actual age at death, because the latter varies with the exigencies of other experiments having no direct connection with the statistical studies. In order to include cancerous mice still living and so increase the volume of the data it was necessary to increase the non-cancerous totals also, by including living non-cancerous mice. These have been included in the age-periods embracing their ages on a selected day (in the case of the present tables, October 24, 1910).

Table I, giving this distribution, and discriminating between cancer of the mamma and cancer of other organs, shows a rapidly increasing proportion of deaths from cancer commencing after six months had passed, attaining a maximum in the three-monthly period ending at 18 months, and then diminishing till, in mice over 24 months old, the frequency is

* In the earlier paper, one mouse was recorded as exactly six months old when the tumour developed. Actually, the tumour was discovered at the age of six months and seven days, and the mouse is therefore entered in the six to nine months age-period in the present tables.

TABLE I. (October 24, 1910.) Female Mice.

Age (months) ...	0–3	–6	–9	–12	–15	–18	–21	–24	Over 24	Total.
No tumour—										
Living	—	—	16	7	7	9	16	9	21	—
Dead	—	—	79	85	63	56	41	37	24	—
Tumour mice—										
Organs other than mamma	—	—	—	1	2	2	2	1	3	—
Mamma	—	—	5	11	16	26	10	8	5	—
Total	—	—	100	104	88	93	69	55	53	562
Per cent. of mammary cancer	—	—	5·0	10·6	18·2	28·0	14·5	14·0	9·4	14·4

barely twice that found in mice under nine months old. Similar figures for the human female give a corresponding curve.

Tables II and III were made after a preliminary distribution of the mice in groups, according as the first cancerous ancestor occurred in the 1st, 2nd, 3rd,... ascending generation, had shown that the majority of the cases of cancer occurred in mice in which either the mother, or a grandmother, or all three, developed cancer.

TABLE II. (24th October, 1910.) Female Mice of Recent Cancerous Ancestry. (Mother, one or both grandmothers, or all three cancerous.)

Age (months) ...	0–3	–6	–9	–12	–15	–18	–21	–24	Over 24	Total.
No tumour—										
Living	—	—	9	7	6	8	7	4	6	—
Dead	—	—	49	48	39	28	22	20	18	—
Tumour mice—										
Organs other than mamma	—	—	—	1	2	2	1	—	1	—
Mamma	—	—	4	7	15	18	10	5	3	—
Total	—	—	62	63	62	56	40	29	28	340
Per cent. of mammary cancer	—	—	6·5	11·1	24·2	32·1	25·0	17·2	10·7	18·2

Table II shows the proportions in which mice of recent cancerous ancestry, in this limited sense, died of cancer at the different age-periods. Table III is to be compared with Table II, and gives the same distribu-

tion for the remaining mice in which the cancerous ancestors are more remote. The curves in fig. 1 show the differences between the percentage of deaths from cancer in the two groups at successive age-periods. The two percentage curves differ very little at the early and at the final periods, but diverge in the middle.

TABLE III. (24th October, 1910.) Female Mice of Remote Cancerous Ancestry. (No cancer in mother or grandmothers.)

Age (months) ...	0-3	-6	-9	-12	-15	-18	-21	-24	Over 24	Total.
No tumour—										
Living	—	—	7	—	1	2	9	5	15	—
Dead	—	—	30	37	24	28	19	17	6	—
Tumour mice—										
Organs other than mamma	—	—	—	—	—	—	1	1	2	—
Mamma	—	—	1	4	1	8	—	3	2	—
Total	—	—	38	41	26	37	29	26	25	222
Per cent. of mammary cancer	—	—	2·6	9·8	3·8	21·6	0·0	11·5	8·0	8·6

Two other curves (fig. 2) constructed in the same way with slightly different limits to the age-period show the same features, except that in the highest age-group (over 25 months in this case) the percentage of deaths from cancer, in the mice of cancerous ancestry, falls just below that in the non-cancerous group (1 in 15 as compared with 1 in 14).

The results of the two distributions agree very closely, and strongly suggest a real difference inherent in the data. Consideration of the factors relegating an animal to one or the other of these two groups (ancestry cancerous, or ancestry non-cancerous) enhances the importance of the difference between them. On the one hand, the cancerous group (Table II) includes many mice with only slight hereditary taint. On the other hand, the mice with non-cancerous ancestry (Table III) are a mixed group; they comprise a certain number which, but for the accident of the early death of parent and grandparents, would have to be added to the group with cancerous ancestry. When a comparison is made between the ancestors of the tumour mice of the non-cancerous group and the ancestors of those which died free from cancer, the ancestors of the tumour mice died in greater proportion in the early age-periods. Hence, if there could be eliminated from the non-cancerous group those mice which are included in

it because of the early death of their female parents and grandparents, tumour mice would be transferred from the non-cancerous group to that with

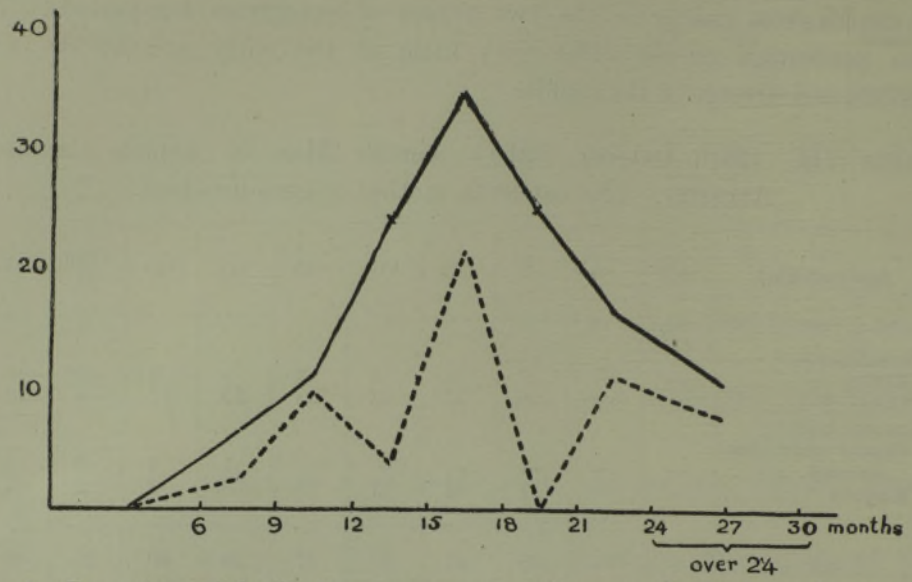

FIG. 1.—Percentage of deaths from mammary carcinoma to deaths from all causes at successive three-monthly age-periods in female mice of recently cancerous ancestry (mother, grandmothers) ——, compared with the same ratio in female mice having more remote cancerous ancestry (mother and grandmothers non-cancerous) - - - - -.

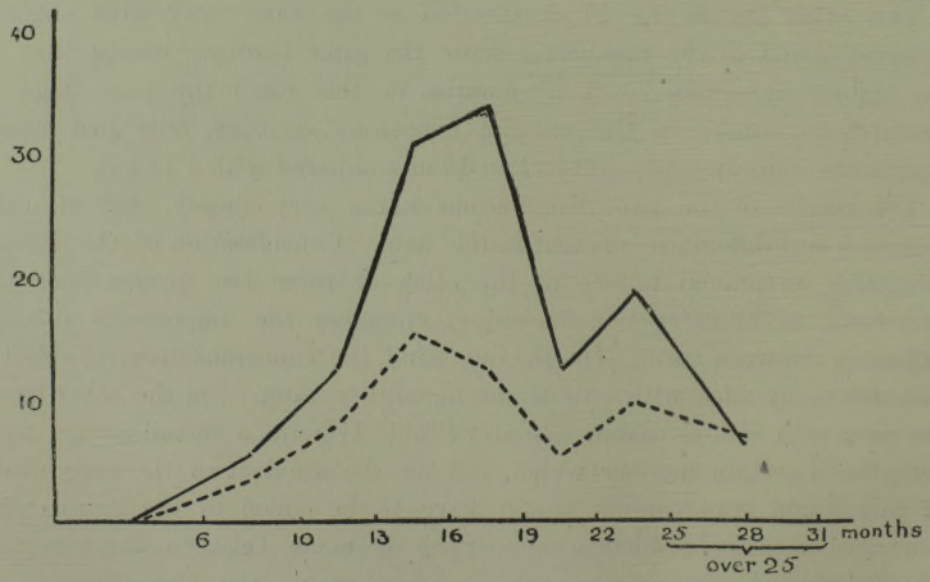

FIG. 2.—The same comparison as in fig. 1, with different limits to the three-monthly age-periods (second period, four months). As in fig. 1, the frequency of the deaths from cancer in the cancerous group exceeds that of the non-cancerous group at all periods except the last.

recent cancerous heredity, in greater proportion than mice which did not develop cancer. In fact, the difference between the two groups is a minimum difference, and it should be possible, by continued selective mating, to breed two strains of mice with a still greater difference in their liability to cancer.

In conclusion, it is well to consider the importance of these results in the light of the comparative pathology of cancer. Investigations of the most diverse kind on man and animals show that the actual initiation of cancer is, in many forms of the disease, a terminal phase of a long-continued process of localised chronic irritation. Even in mice in whose ancestry cancer is absent, cancer may arise in consequence of such irritation, particularly when they attain extreme old age, in large numbers, and a diminished predisposition to the disease would merely effect a diminution in the number of individuals attacked as compared with a corresponding number of individuals with inherited liability similarly irritated. The phenomena of the experimental production of sarcoma by transformation of the stroma of transplanted tumours of a particular strain in nearly all animals, however, indicate that the diminished liability is never likely to become absolute in practice. Conversely, it should be possible by shielding individuals, even of highly susceptible stock, from chronic irritation of specific tissues to diminish considerably the incidence of cancer of these tissues amongst them.

Other investigations have shown that a constitutional condition favouring the *growth* of cancer and accounting for its incidence is not present in mice which suffer spontaneously from the disease. The determining factors are those which *initiate* cancerous proliferation, and it is highly probable that the predisposing condition which is transmitted is some peculiarity of the cells of the tissues in which cancer develops, of such a kind that, under the wear and tear of life, the regenerative and proliferative changes which accompany the inception of the disease are more prone to occur, or take place with greater intensity. The present observations harmonise with the conclusion drawn from other lines of work, that cancer always arises *de novo* in the organism attacked by a transformation of the ordinary tissue elements, and lend no support to the view that groups of cells outside the anatomical and physiological nexus of the organism from an early period in the ontogeny form the physical basis of the development of malignant new growths.

The figures have also been submitted to mathematical analysis, involving determination of the standard errors of the differences between the cancerous

and non-cancerous groups. Taking the crude data, the actual percentages amongst all the offspring are :—

Ancestry cancerous	18·2 per cent.
Ancestry non-cancerous	8·6 „
Difference	9·6 „

these percentages being based on 340 and 222 cases respectively. When a correction is made for the varying age-distributions of the two groups by calculating corrected percentages based on the age-distribution of all mice and reducing the numbers to the corresponding proportions per thousand, the difference is merely slightly increased from 9·6 to 9·8 per cent. The standard error of this difference is 2·96. The difference is 3·3 times the standard error, and the chance of its occurring as a mere fluctuation of random sampling only about 1 in 1000.

The following are the differences for the separate age-classes, with their standard and probable errors :—

Age.	Difference.	Standard error.	Probable error* = 0·6745 standard error.
– 9	3·9	4·49	3·03
–12	1·3	6·18	4·17
–15	20·4	9·02	6·08
–18	10·5	7·98	5·38
–21	25·0	8·59	5·79
–24	5·7	9·51	6·41
24–	2·7	8·03	5·42

* The probable error is the fluctuation of sampling that will be as often exceeded as not.

It will be seen that four of the seven differences exceed their probable errors, but the only differences that do so at all considerably are those for the three central age-groups. The difference between the two groups is almost certainly significant, *i.e.* not due to mere fluctuations of sampling.