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Correlation Between Mendelian Rescessive Traits and the Resistance to Fibrosarcoma in Mice

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A C K N O W L E D G E M E N T S

This thesis represents work done in the Mouse Laboratory of the Department of Anatomy of the Yale University School of Medicine during the years 1950 to 1953. During this time, the author has had the pleasure and privilege of a close association with Dr. Leonell C. Strong, who has generously provided facilities, suggestions, funds, and encouragement for the completion of the work herein described.

To Mrs. L.C. Strong, special thanks are extended for her invaluable work in preparing the graphs.

To my wife, I am grateful and sympathetic for the hours of proof reading and typing the many copies of this thesis.

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INTRODUCTION

The influence of heredity on the induction of tumors in experimental animals has received wide attention from investigators in many laboratories. Information has accumulated in the past forty years which warrants a conclusion that a predisposition to cancer, or a sensitivity of the tissues to become cancerous, is inherited in some fashion. Reinhard and Candee (13), as well as Strong (22), Andervont (2), Boyland and Warren (4), and others, have shown that strains of mice vary in their susceptibility to carcinogen-induced tumors.

If the human organism is found to react to disease in exactly the same way as certain animals do, such as mice, we would be justified in holding the same conceptions concerning the nature of neoplasms as are held by the many geneticists working in the field of cancer in experimental animals. We are inclined to believe that, as regards human beings, statistics so far are unable to demonstrate any such condition as those in mice referred to, but it is one of those matters that time and proper study of cases and their classification will finally clear up.

Andervont (3), Strong (23), and others have found an intermediate susceptibility of the F_1 generation to carcinogenic agents when compared with the parent strains.

The problem of this investigation is to determine the susceptibility of the F_1 generation and that of the backcross to the recessive parent, and to correlate these facts with the older data from other investigations.

MATERIALS AND METHODS

Two pedigreed strains of mice provided by Dr. L.C. Strong have been used in this investigation, the pBr and the I strains, in addition to several hybrid generations resulting from the crossbreeding and the backcross of mice of these two original strains. The origin of the pBr and I strains will be discussed only briefly here. Strong separated the pBr line from the original NHO strain in the F_{14} generation of brother-sister mating. The NHO line was originated by cross of mice of the JK and N ancestral stocks. pBr mice have the genes for pink eye, brown coat, and non-agouti. This line is now in the F_{44} generation of sib mating. The I strain originated in the laboratory of Dr. W.E. Castle at Bussey Institute, Harvard University. At that time the mice were not inbred, but have been continued in sib matings by Strong for fifty-five generations.

Tables I, II, and III describe the mice used in these studies as well as their genetic constitutions and relationships. The total number of mice used in the investigation was 1621, including animals used for breeding of the new hybrid mice. Inspection of Tables I and II shows that the only difference amongst the several strains studied is the dominance or recessiveness of the genes at the S-s and D-d loci.

Concerning the use of mice of inbred strains, Strong (33) reports that through attainment of reproducible results and statistical analysis of data biological variability within a particular strain has been reduced to a minimum. This fact has been shown over and over again, and for this reason biological research can be placed on a quantitative basis.

Table I Synthesis of the mouse groups used in the investigation

Parental Strain	Offspring Designation
pBr male x I female	F_{1a}
I male x pBr female	F_{1b}
F_{1b} male x I female	F_{2a}, F_{2b}, F_{2c}, F_{2d}
I male x F_{1b} female	F_{2f}, F_{2g}, F_{2h}, F_{2e}

Table II Genetic constitution of the mouse groups used in the investigation

Strain	Genotypes
pBr	aappbbSSDD
I	aappbbssdd
F_1	aappbbSsDd
F_{2a}, F_{2e}	aappbbSsDd
F_{2b}, F_{2f}	aappbbSsdd
F_{2c}, F_{2g}	aappbbssDd
F_{2d}, F_{2h}	aappbbssdd

Table III Genetic symbols and their effect upon the mice discussed in this paper

Genetic Symbol	Phenotype
B	black coat
b	brown coat
P	dark eye
p	pink eye
S	self
s	piebald
D	non-dilute (intense)
d	dilute
A	agouti
a	non-agouti
C	non-albino (colored)
c	albino
c^{ch}	chinchilla
Se	long ear
se	short ear
w	white belly

One milligram of methylcholanthrene dissolved in 0.1 cc. of sesame oil was injected subcutaneously into the right fore flank of the animal at sixty days of life. The oil has previously been tested and found to be noncarcinogenic by Andervont (2) and others (6). Gardner (7), however, reported four cases of sarcoma arising from the use of sesame oil itself, but these results have not been verified by any other investigator. Several other media have been tried by others (2) for methylcholanthrene with no resulting influence on the carcinogenicity of the compound. The animals were then examined weekly for evidence of tumor growth by the same observer throughout the investigation, and the time at which the tumor first appeared was recorded. The latent period was taken to be the time interval expressed in days between injection of the carcinogenic agent and the palpation of a definite tumor. All mice dying or killed during the experiment were examined at autopsy and all lesions were fixed in Bouin's fixitive and stained with hematoxylin and eosin.

The experiment was continued until all mice had either died or developed tumors. The data include analysis of the appearance of all local tumors, and do not attempt to classify them into specific types, although fibrosarcoma appears to be the tumor seen in the majority of cases. Grüneberg (8) reports that no strain of mice has yet been described in which spontaneous tumors of the skin and subcutaneous tissue is common with any great incidence. No spontaneous tumors, except adenocarcinoma of the mammary gland, have been obtained by Strong (33) who has kept a colony of control animals for the strains used in the present work over a period of many years. Therefore, we may exclude spontaneous tumors as a source of error in this investigation.

The mice were given a diet of nurishmix with an unlimited supply of water, and housed in a room with temperature controlled at 70-73 degrees F. and with humidity controlled at 50-60 percent. They were kept five or less mice in each side of a double box and were not allowed to breed.

In addition to controlling the pedigree of the animals, the litter seriation phenomenon as shown by Strong (26) has been taken into account. For this reason, only mice from the first, second, and third litters of a particular mating were used in the investigation. Furthermore, the lineage has been selected toward early litters for several generations. This precaution will offset any variability which might have appeared if animals of later litters had been used either as breeders or experimental animals.

RESULTS

The data obtained on the incidence of local tumors* and the latent periods of the several strains of mice are given in Table IV. There is marked similarity of the incidence percentage and the medians of the latency periods of those mice bearing the same number of recessive genes in their genetic makeup. This is in sharp contrast to those data from mice with different numbers of recessive genes. There should be noted the difference in the correlation when using the median as opposed to using the mean values. The median result in these types of data is probably a more reliable measure since in utilizing the median a few mice developing tumors at a very early or very late age will not cause the true value to be misleading, whereas the average value (mean) may so become. In determining the probable error of the median, the formula used is :

$$\text{P.E.} \pm \frac{\text{average deviation quartiles } (Q_3 - Q_1/2)}{\sqrt{N}}$$

The rates at which local fibrosarcomas appeared in mice of each group are shown in Figures 1 through 12. In each case data for the male mice are given on the dotted line; data for the female mice are plotted on the solid line.

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*In this paper, following the example of Strong (25), the term local tumor applies to all tumors that arise at the site of injection of methylcholanthrene. In contrast to Strong, however, who analyzed the effect of litter seriation on fibrosarcoma alone, these tumors include fibrosarcoma, epidermoid carcinoma, rhabdomyosarcoma, and a few carcinomas of the mammary gland. This classification is not the usual one, but is based on the genetic concept that the only manner by which a gene can be identified is by its effect upon the organism. Therefore, if there be any genetic factor in common to several or all neoplastic growths, it can be identified only by classifying all types of tumors together.

Table IV Latency period in days for all groups of mice investigated*

Designation and Genotype		Median	Mean	Number of Mice	Percent Tumors
pBr(SSDD)	male	190±11.5	241	40	80
	female	150± 9.5	166	40	80
F_{1a}(SsDd)	male	210±15.3	228	46	43.5
	female	187±15.7	207	50	48
F_{1b}(SsDd)	male	200± 8.8	210	49	53.1
	female	170± 5.4	175	55	52.7
F_{2a}(SsDd)	male	216±10.8	224	40	47.5
	female	188±24.2	201	40	52.5
F_{2b}(Ssdd)	male	228± 9.2	240	48	35.4
	female	215±11.8	219	45	37.8
F_{2c}(ssDd)	male	229±13.7	252	55	34.5
	female	214±15.4	202	44	36.4
F_{2d}(ssdd)	male	245±11.4	253	80	21.3
	female	235±13.4	243	70	21.4
F_{2e}(SsDd)	male	210± 8.2	219	39	53.8
	female	191± 8.9	203	36	52.8
F_{2f}(Ssdd)	male	225±10.7	235	40	37.5
	female	220± 9.7	219	40	37.5

Table IV (Con't.)

Designation and Genotype		Median	Mean	Number of Mice	Percent Tumors
F_{2g}(ssDd)	male	228±10.5	229	46	36.9
	female	218± 7.6	214	55	38.2
F_{2h}(ssdd)	male	235±10.2	243	60	25
	female	225± 9.8	229	65	29.6
I(ssdd)	male	240±29.1	288	100	20
	female	235±25.5	259	90	22.5

*Both the median and the mean values are expressed in the table, but in this type of analysis use of the median is more suited, as is explained in the text.

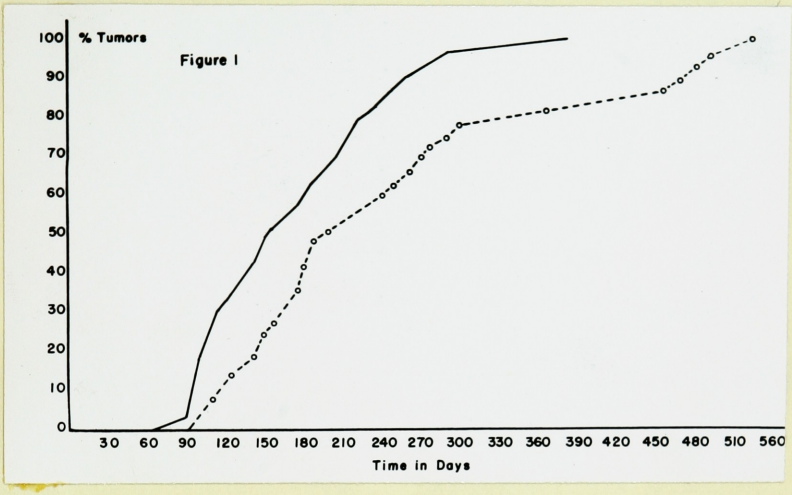

Figure 1 Cumulative data on a) female mice of the pBr (SSDD) strain on solid line; and b) male mice of the pBr strain on dash line. Time in days expressed along the base line; cumulative percentage of tumors among tumor bearing mice at the site of injection expressed along the vertical line.

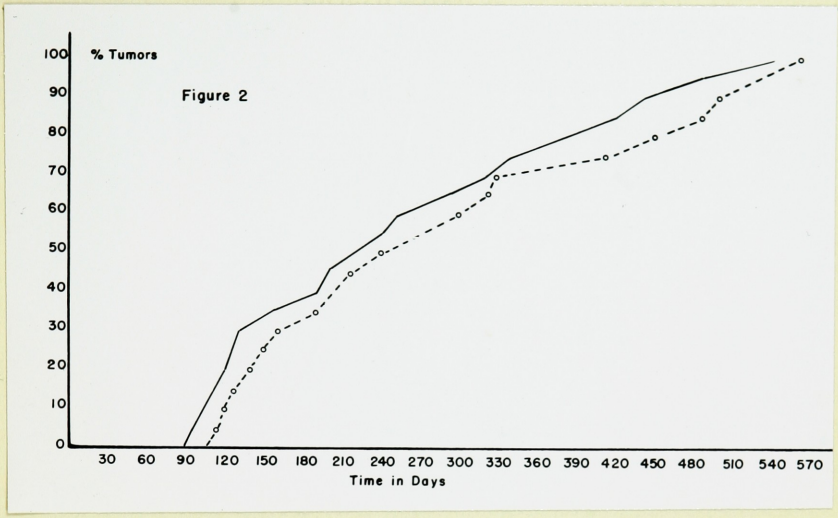

Figure 2 Cumulative data on a) female mice of the I (ssdd) strain on solid line; and b) male mice of the I strain on dash line.

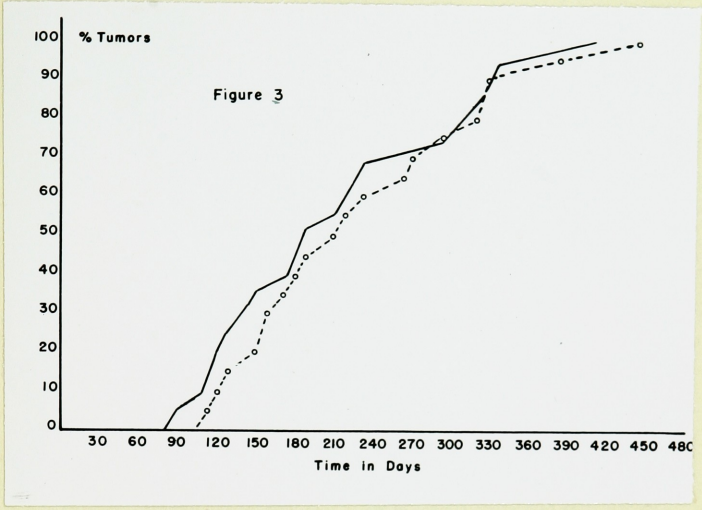

Figure 3 Cumulative data on a) female mice of the F_1a (SsDd) strain on solid line; and b) male mice of the F_1a strain on dash line.

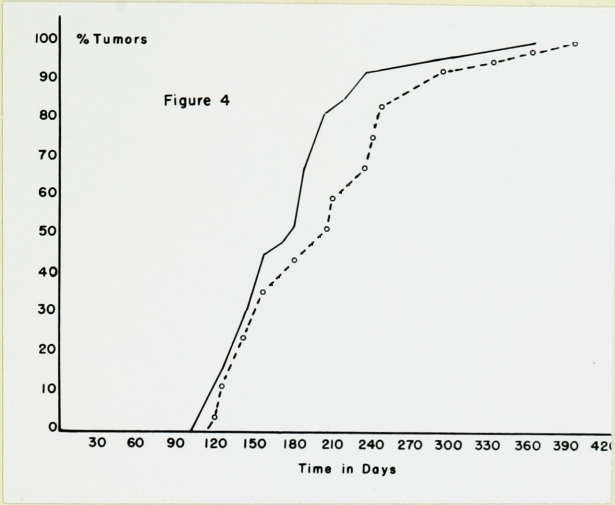

Figure 4 Cumulative data on a) female mice of the F_1b (SsDd) strain on solid line; and b) male mice of the F_1b strain on dash line.

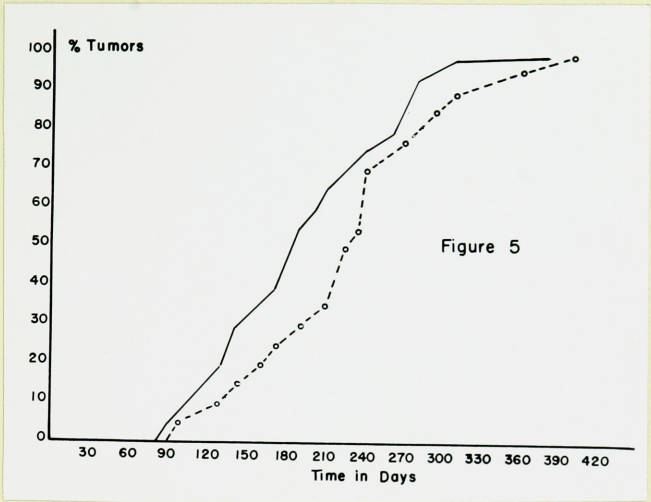

Figure 5 Cumulative data on a) female mice of the F_2a (SsDd) strain on solid line; and b) male mice of the F_2a strain on dash line.

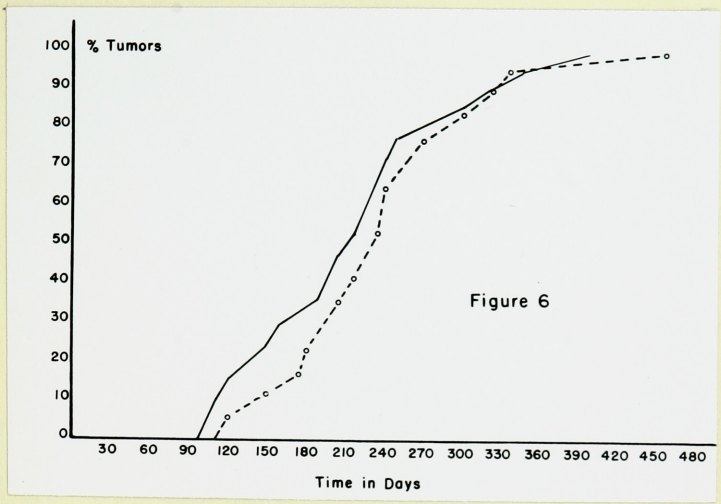

Figure 6 Cumulative data on a) female mice of the F_{2b} (Ssdd) strain on solid line; and b) male mice of the F_{2b} strain on dash line.

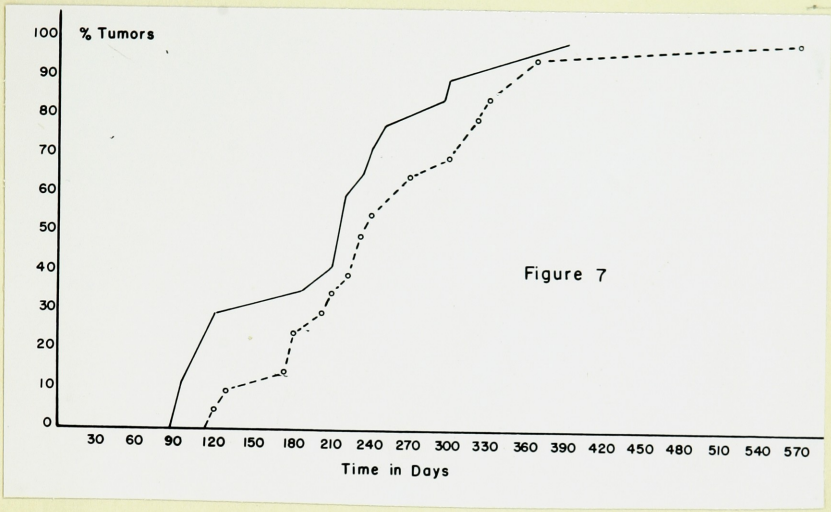

Figure 7 Cumulative data on a) female mice of the F_{2c} (ssDd) strain on solid line; and b) male mice of the F_{2c} strain on dash line.

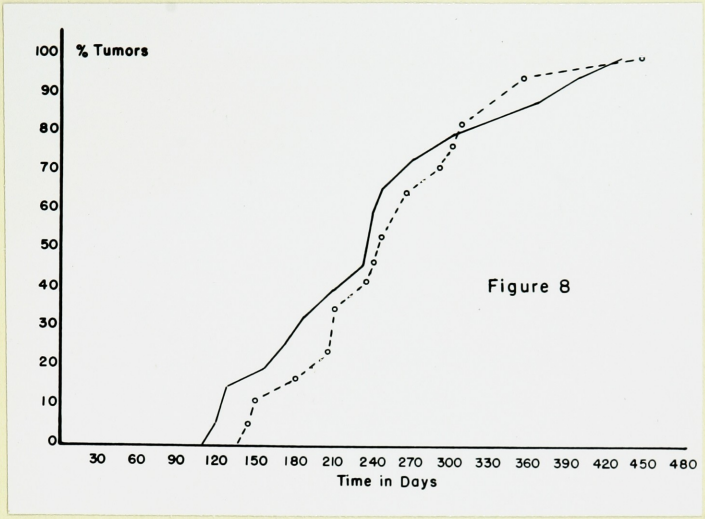

Figure 8 Cumulative data on a) female mice of the F_{2d} (ssdd) strain on solid line; and b) male mice of the F_{2d} strain on dash line.

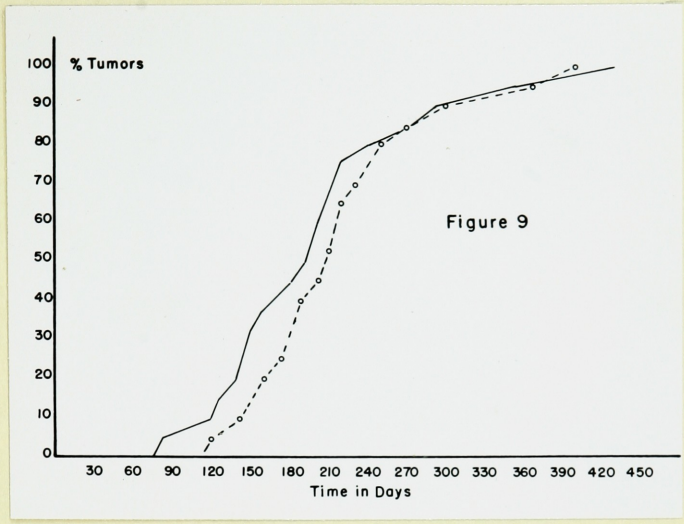

Figure 9 Cumulative data on a) female mice of the F_{2e} (SsDd) strain on solid line; and b) male mice of the F_{2e} strain on dash line.

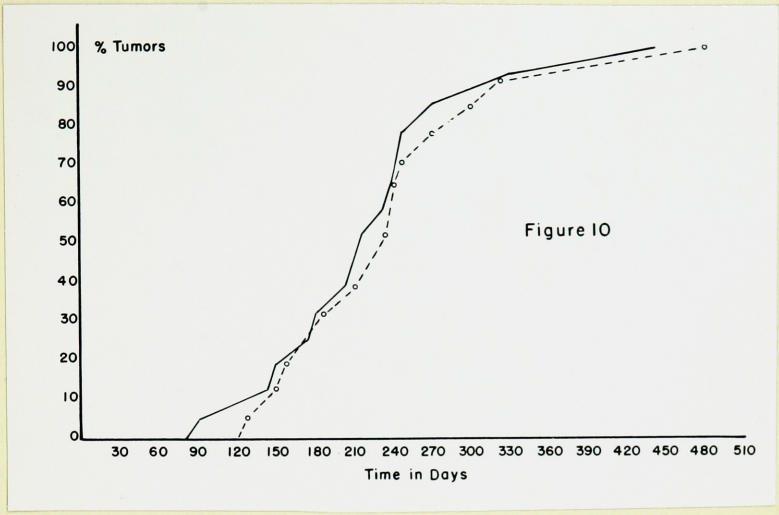

Figure 10 Cumulative data on a) female mice of the F_{2f} (Ssdd) strain on solid line; and b) male mice of the F_{2f} strain on dash line.

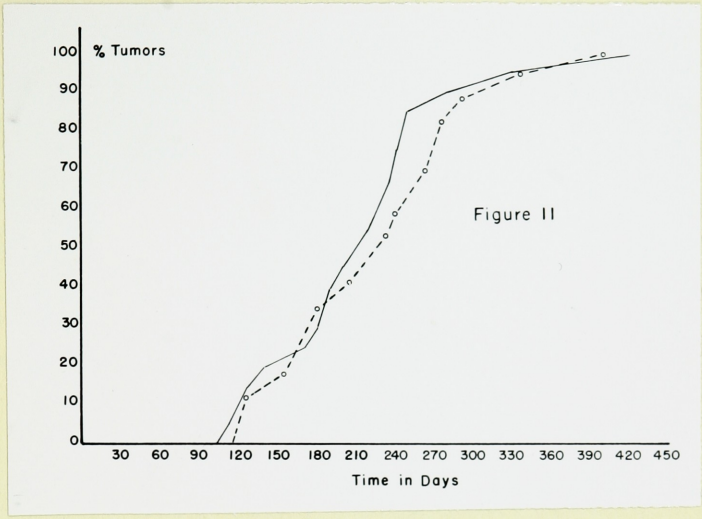

Figure 11 Cumulative data on a) female mice of the F_{2g} (ssDd) strain on solid line; and b) male mice of the F_{2g} strain on dash line.

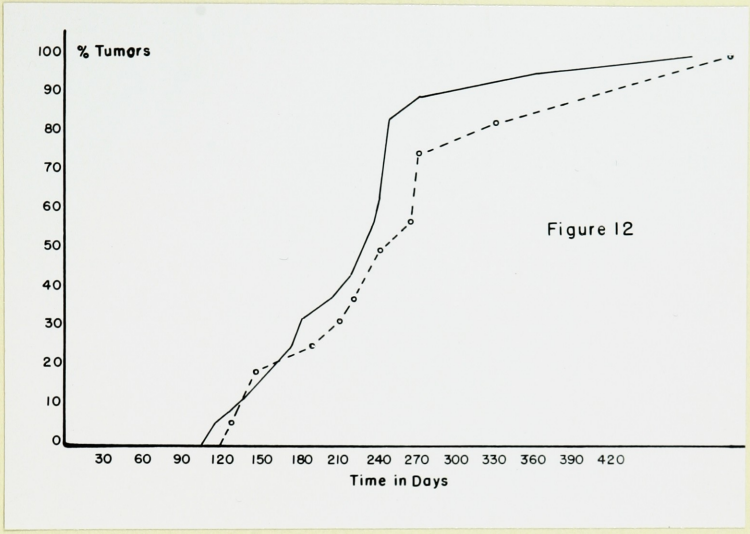

Figure 12 Cumulative data on a) female mice of the F_{2h} (ssdd) strain on solid line; and b) male mice of the F_{2h} strain on dash line.

Figure 13 compares the data obtained from the F_1 generation (F_{1a} and F_{1b}). In this graph, the F_{1a} male and female mice are shown on the solid line and the long dash line respectively, and the F_{1b} mice on the open circle-solid line and open circle-dash line respectively.

Figures 14 and 15 present the data obtained from the second and third quartiles and plotted for all groups of mice in the parental and offspring generations, the males being shown in Figure 14 and the females in Figure 15. Data for the original pBr and I mice are given on the solid line and on the dotted line. Data for the F_{2a}, F_{2b}, F_{2c}, and F_{2d} mice are given on the dot-short dash line, the short dash line, the long dash line, and the dot-long dash line. Data for the F_{2e}, F_{2f}, F_{2g}, and F_{2h} mice are given on the open circle-solid line, closed circle-long dash line, open circle-short dash line, and the open circle-dot-dash line. In Figures 1 through 13, the data are complete only to the point indicated.

If we group the mice according to the number of recessive genes in the genetic structure, we may show the relationship between the number of recessive genes and the resistance to chemically-induced local tumors. In Figure 16 each genic class of males is plotted; in Figure 17 the female genic classes are shown. In this manner we see the effect of adding more recessive genes on the resistance, and we also see a qualitative difference between individual recessive genes. Thus the piebald gene seems to impart more resistance than the dilute gene, an observation also found in some of Strong's (21) work.

In all cases, the cumulative percentage of mice showing tumors is given on the vertical line; the time in days is given on the base line.

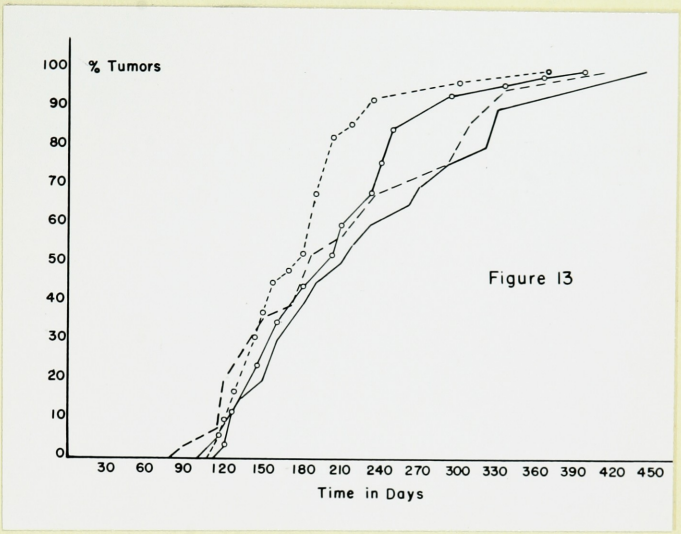

Figure 13 Cumulative data on a) female mice of the F_{1a} (SsDd) strain on dash line; b) male mice of F_{1a} strain on solid line; c) female mice of F_{1b} (SsDd) strain on open circle-dash line; and d) male mice of F_{1b} strain on open circle-solid line.

Figure 14 Cumulative data of the second and third quartiles of male mice: pBr (SSDD) strain on solid line; I (ssdd) strain on dotted line; F_{2a} (SsDd) on dot-short dash line; F_{2b} (Ssdd) on short dash line; F_{2c} (ssDd) on long dash line; F_{2d} (ssdd) on dot-long dash line; F_{2e} (SsDd) on open circle-solid line; F_{2f} (Ssdd) on closed circle-long dash line; F_{2g} (ssDd) on open circle-short dash line; F_{2h} (ssdd) on open circle-dot-dash line.

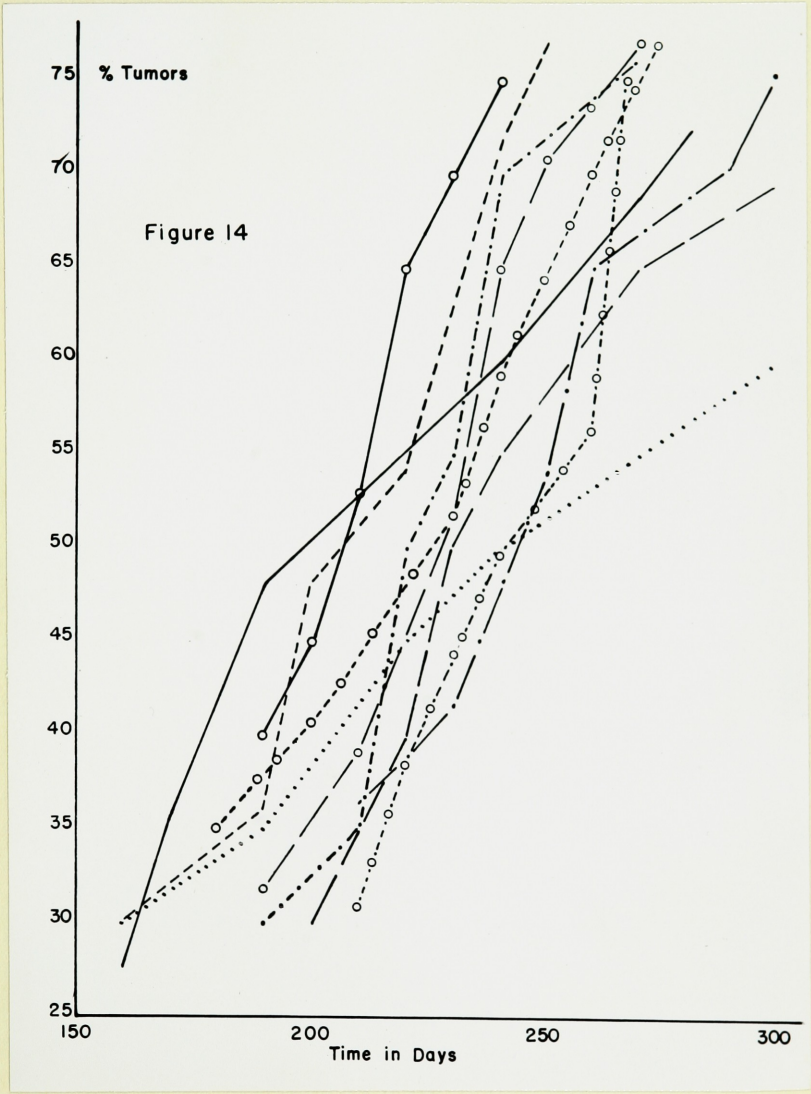
75
% Tumors
70
65
60
55
50
45
40
35
30
25
150
200
250
300
Time in Days

Figure 14

Figure 15 Cumulative data of the second and third quartiles of female mice: pBr (SSDD) strain on solid line; I (ssdd) strain on dotted line; F_{2a} (SsDd) on dot-short dash line; F_{2b} (Ssdd) on short dash line; F_{2c} (ssDd) on long dash line; F_{2d} (ssdd) on dot-long dash line; F_{2e} (SsDd) on open circle-solid line; F_{2f} (Ssdd) on closed circle-long dash line; F_{2g} (ssDd) open circle-short dash line; F_{2h} (ssdd) on open circle-dot-dash line.

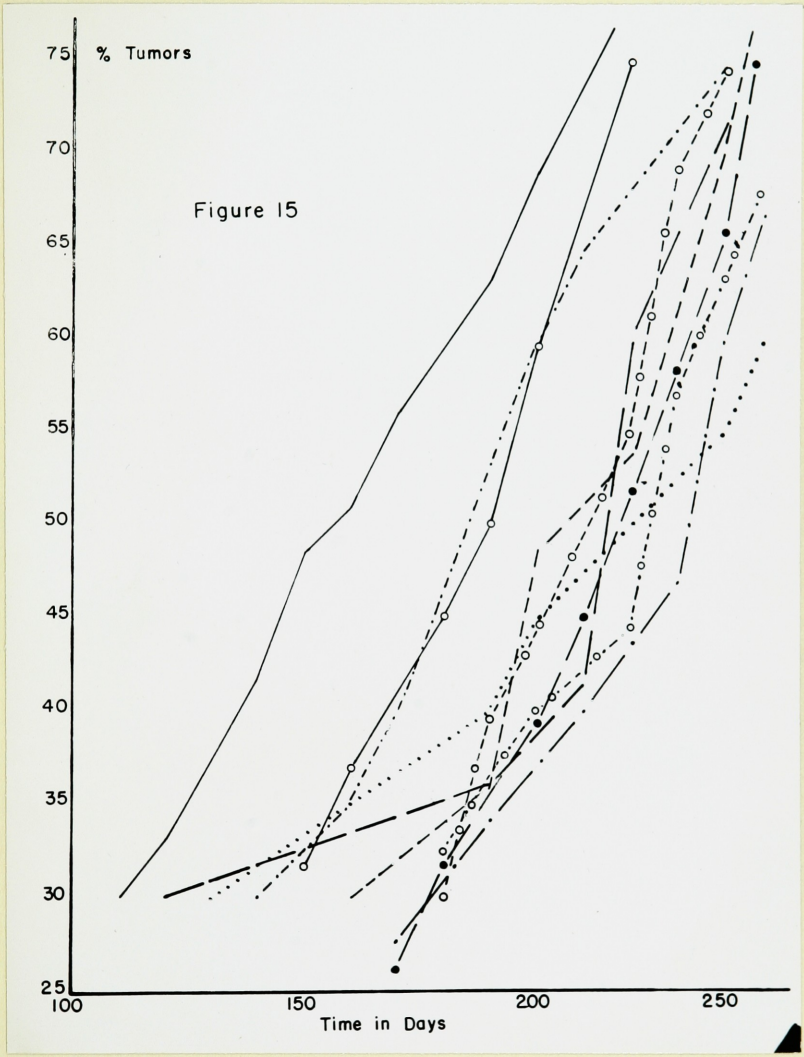
% Tumors
75
70
65
60
55
50
45
40
35
30
25
100
150
200
250
Time in Days

Figure 15

Figure 16 Cumulative data of the second and third quartiles adding the genic classes of male mice together: pBr (SSDD) on solid line; I (ssdd) on dotted line; SsDd on short dash line; Ssdd on long dash line; ssDd on open circle-solid line; ssdd on open circle-dash line.

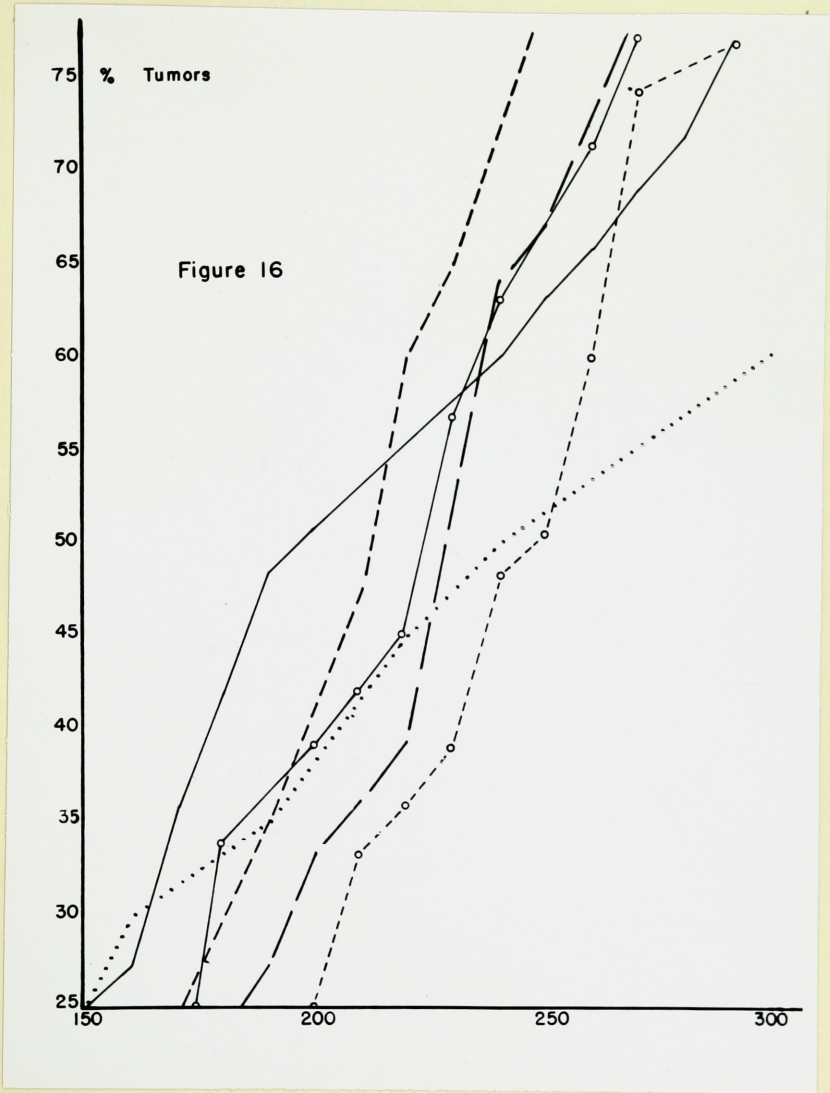

Figure 16

Figure 17 Cumulative data of the second and third quartiles adding the genic classes of female mice together: pBr (SSDD) on solid line; I (ssdd) on dotted line; SsDd on short dash line; Ssdd on long dash line; ssDd on open circle-solid line; ssdd on open circle-dash line.

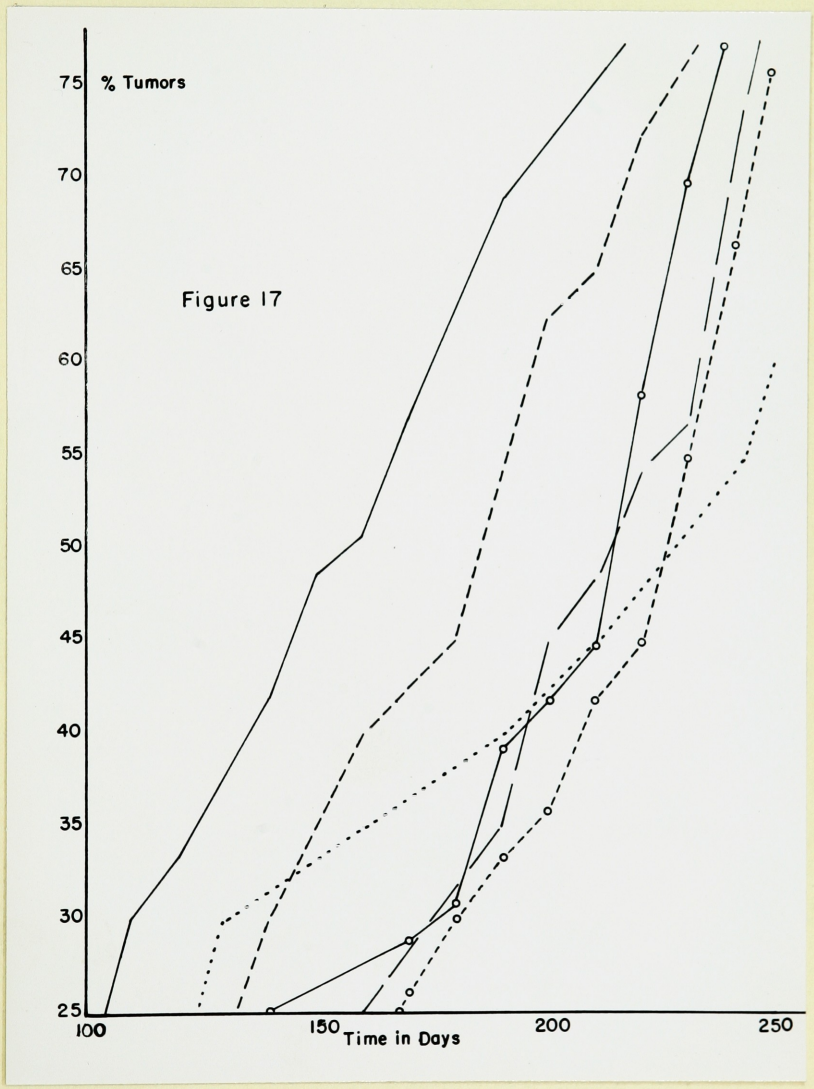
75
% Tumors
70
65
60
55
50
45
40
35
30
25
100
150
Time in Days
200
250

Figure 17

DISCUSSION

The process of carcinogenesis is one in which there seems to be three variables: 1) the genetic makeup of the tissues affected; 2) the extragenetic environment, such as litter number, sex, age, hormone balance, etc; and 3) some physiologic or pathologic imbalance or irritation caused by an alteration in the tissue metabolism, either naturally or experimentally induced.

The evidence is accumulating that the appearance of a local tumor arising at the site of injection of methylcholanthrene is determined, to a great extent, by the constitutional state of the individual, which is, in turn, under genic control as well as some other force as measured by litter seriation. Strong (21) expresses the opinion that the genes involved in local tumor susceptibility are probably few in number. He has found one of these to be in linkage relationship with the brown coat gene and another with the piebald gene. Maud Slye (14, 15) proposed that spontaneous cancer behaves as a simple Mendelian recessive. In addition, using well pedigreed stocks but also, according to Little (11), questionable genetic thinking, she feels that the type of tumor, as well as the location of tumor formation, are also inheritable. Lathrop and Loeb (10) and Lynch (12) found in their sets of series cancer to behave as a Mendelian dominant. Reinhard and Candee (13) and also Kreyberg (9) have shown a longer latent period before tumor formation in the male in contrast to the female. On the other hand, Branch (5) found no significant difference between C57 males and females.

The resistance of a strain is determined by the period of time elapsing between injection of the carcinogenic agent and the appearance

of the tumor, i.e., the latent period, and the percentage of mice developing tumors. These factors are related to the amount of carcinogen used, the potency of the carcinogen, and the genetic uniformity or variability of the experimental animals. Strong (26) has shown recently that the litter number to which the mice belong, i.e., the age of the mother at the time of birth of the mice, is an important factor in the length of the latent period, presumably due to extrachromasomal factors which influence the susceptibility to fibrosarcoma.

Andervont (3) has reported that the F_1 generation derived from mating C_3H to I strains and C_3H to Y strains were of intermediate susceptibility when compared with the susceptibility of the parent strains. Strong (23) has found similar results with other strains. In addition, he (33) established the following relationship amongst several strains in order of increasing resistance: black coat (B), brown coat (b), pink eye (p), pink eye brown (pBr), and I strains. It occurred to the writer that each succeeding strain of the group differed from the one directly above it by only one gene in its genetic makeup. Further, the gene is recessive to the one on the same locus of the strain immediately above on the curve of increasing resistance. Thus b strain differs from B strain only in having the recessive gene for coat color instead of the dominant one. p differs from b strain in having the recessive gene p for eye color instead of the dominant P gene. pBr strain differs from p strain in the gene for coat color, pBr having the recessive b gene. I strain (ppbbssdd) has the recessive genes ssdd instead of the SSDD genes of pBr.

Synthesis of these observations allows a relationship to be built and correlated with resistance to tumor formation by methylcholanthrene. The most likely answer to these facts seems to be that a recessive gene imparts more resistance than a dominant gene. In addition, the process seems to be an additive one. Therefore, a strain with two recessive genes has greater resistance than one with only one, etc. For that reason the I strain with four recessive gene loci more than the B strain should be many times more resistant to tumor formation.

The actual mechanism of the correlation between recessive genes and resistance is, of course, open to much speculation, but Strong (22) suggests one very plausible hypothesis. He has shown that a gene S^{fs} (susceptibility to fibrosarcoma) is in linkage relationship with the dominant black coat gene B. Arguing from this, we may postulate several genes similar to the S^{fs} gene which are linked to other genes, predominantly dominant ones. These S (susceptibility) genes should obey the same laws of Mendelian heredity (linkage and crossover) as others as we know them. In this structure, recessive genes for coat color, eye color, etc. would be linked with recessive genes for resistance to fibrosarcoma (s^{fs}).

The present investigation has been set up to test this hypothesis structure. In analyzing the results it can be seen that the F_1 generation is intermediate in susceptibility to that of the parental generations which is also shown by others (3, 23), and which is in accordance with the present hypothesis. The difference in latent periods between the F_{1a} and the F_{1b} strains is not statistically significant, probably due

to the small numbers of animals involved, but is certainly suggestive of some difference. Concerning the reason for this, we may speculate that the strain (F_{1a}) which has for its mother an animal from a highly resistant strain (I) receives some extra resistance factor through an unknown extragenetic factor, while the strain (F_{1b}), mothered by a susceptible line (pBr), may not receive this factor in as great a quantity, etc. and is therefore somewhat less resistant. This difference could also be explained, so far, on X-linked inheritance.

In the backcross to the recessive there is also a general trend exhibiting this maternal effect, but again it is not statistically significant. Not only is there segregation in the backcross to four different classes of phenotypes and genotypes in the expected 1:1:1:1 ratio, but there is also the same segregation in tumor susceptibility. And, what is more significant, the various classes behave as expected according to the hypothesis. Thus, F_{2a} and F_{2e} which are identical genetically with F_{1a} and F_{1b} (SsDd) have latent periods which are almost identical (the differences not being statistically significant). The F_{2b} and F_{2f} (Ssdd) classes which are intermediate to the F_1 and the I strains in respect to the number of recessive genes in the genetic makeup are found to be also intermediate in their latent periods. In the same fashion are the F_{2c} and F_{2g} (ssDd) classes the same. The F_{2d} and F_{2h} (ssdd) classes, identical with the I strain in genetic makeup, have latent periods very closely approximate to that of the I strain.

A curve may be established demonstrating the relationships among the various strains used in this experiment and shown in Figures 13, 14,

and 15.

Thus we have succeeded in establishing several intermediate points in the resistance relationship among the several strains as determined by Strong (33) and discussed above, and have succeeded in establishing a workable hypothesis of the inheritance of tumor susceptibility and resistance.

In analysis of the literature one may explain the greater susceptibility of one strain over another in many workers' series by the present hypothesis. Strong (22) reports the mutation of brown (recessive) coat color to one of black (dominant) with the concommitant large increase of susceptibility to fibrosarcoma induced at the site of methylcholanthrene injection. Burdette and Strong (6) demonstrated resistance relationships in several strains of mice as shown in Figure 18. The genetics of these strains are characterized in Table V. Here again the series follows the general pattern of the relationship of resistance to the recessiveness (or number of recessive genes in the genetic constitution).

Andervont has done a great deal of work in experimental cancer genetics. His (2) series of strains together with their genetic makeup and resistance relationship is shown in Table VI. He found, as have many other workers in the past, that the C_3H strain of mice was very susceptible to tumor induced by carcinogenic hydrocarbons, and the I strain was very resistant. Between these extremes he found the C, M, C_{57}, A, and D strains in that order of relative increasing resistance to tumor formation. Inspection of the genotype relations reveals a general increase

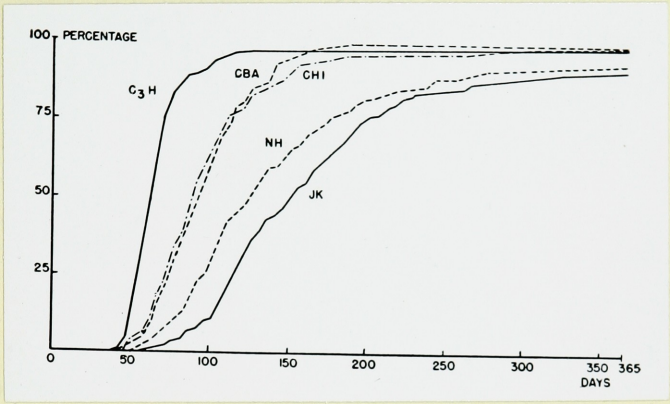

Figure 18 Time from injection to appearance of tumors in five inbred strains, from Burdette and Strong (6).

Table V Genic makeup of the animal strains analyzed by Burdette and Strong (6)

Strain	Genotype
C_3H	AABBCCDDPPSSSeSe
CBA	AABBCCDDPPSSSeSe
CHI	AABBCCDDPPSSSeSe
NH	AABBCCddppssSeSe
JK	aabbCCDDppSSSeSe

Table VI Genetic makeup of animal strains analyzed by Andervont (2)

Strain	Genotype
C_3H	AABBCCPPDDSSSeSe
C	AAbbCCppDDSSSeSe
M	aabbCCPPDDSSSeSe
C_{57}	aaBBCCPPDDSSSeSe
A	aabbccPPDDSSSeSe
D	aabbCCPPddSSSeSe
I	aabbCCppddssSeSe

in the number of recessive genes as the resistance increases, in accordance with the present hypothesis.

What is the significance of the recessive tendency in the genetic control of resistance of tumor formation? It may mean the hereditary transmission of greater or lesser resistance to the causative factors is involved in the mutation or change in cell metabolism, whether these factors be hormones, viruses, carcinogenic agents (chemicals), or any other form of chronic irritation. Or it may mean that the susceptibility factor is associated with the genetic dominant traits of an individual and resistant factor with the recessive traits. Or it may mean that genetics can control the production of an individual or of an organism with a greater or lesser degree of resistance to malignant disease, or even to all disease. As far as cancer inheritance is concerned, however, Strong's work on the litter seriation phenomenon shows that two animals identical in their genetic makeup, but differing in the age of their mother at the time of their birth, i.e., of different litters, behave differently and have different degrees of susceptibility to tumor formation. From this fundamental stride forward in our genetic thinking the conclusion can be drawn that the susceptibility to cancer is at least partly controlled by extrachromosomal or cytoplasmic elements. In addition, from the work of the present investigation and its apparent corroboration amongst the literature, the conclusion can be drawn that the resistance to cancer is at least partly associated in experimental animals with the cumulative recessive traits of the individual.

SUMMARY

1. A correlation between tumor resistance, as measured by the latency period and the percentage of animals acquiring tumors, and the number of recessive genes in the genotypic makeup has been investigated with methylcholanthrene-induced tumors in mice.

2. Evidence is presented which points to the fact that recessive genes impart more resistance than dominant ones. In addition, the relationship seems to be an additive phenomenon, i.e., the more recessive genes in the makeup of the animal, the greater the resistance.

3. The results of this study are discussed in light of the findings of various other investigators, and these seem to fit in well with their findings.

4. A speculative hypothesis of mechanism is presented and discussed.

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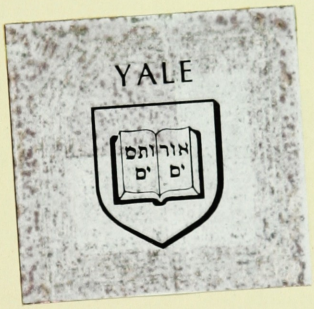
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