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MAMMARY TUMOURS IN HYBRID MICE: THE PRESENCE AND TRANSMISSION OF THE MAMMARY TUMOUR AGENT.

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A PREVIOUS paper (Foulds, 1947) recorded the origin in hybrid mice of spontaneous mammary tumours, many of which were transplantable in female or oestrogenized male hosts but not in normal males. The present paper is concerned primarily with evidence for the presence and transmission of the mammary tumour agent. Two succeeding papers (Foulds, 1949*a*, *b*) deal with the responsiveness of transplanted and of spontaneous mammary tumours to hormones.

The hybrid mice which provided the hormone-responsive transplantable

tumours were obtained by mating females of the low mammary tumour strain C57 black with males of the high mammary tumour strain R3 and were described briefly as CR hybrids. To conform with the more usual practice of using "B" as the abbreviation for C57 black and to avoid confusion with the "C" strain used by American workers, the designation BR F_1 is now applied to the (C57 black ♀ × R3 ♂) F_1 hybrids and RB F_1 to the reciprocal hybrids (R3 ♀ × C57 black ♂) F_1 . Thus BR and RB correspond with CR and RC respectively in the earlier paper.

The present investigations provide evidence for the presence of tumour agent in BR F_1 hybrids, although these mice were nursed by their C57 black mothers presumed deficient in tumour agent. They show that spontaneous mammary tumours developed abundantly in the progeny of two tumour-bearing BR F_1 females, and that extracts of a transplanted BR F_1 tumour induced the growth of mammary tumours in other hybrids deficient in the tumour agent. Further observations on BR F_1 hybrids are recorded, and a high incidence of tumours in the reciprocal RB F_1 hybrids is described. Finally it is shown that the incidence of tumours in BR F_1 hybrids is greatly reduced or delayed when the male parent is derived from a line of R3 mice freed from the tumour agent.

Mammary tumours in BR F_1 mice.

Amongst the survivors of the BR F_1 colony described in the earlier report (Foulds, 1947), three breeding females and two virgins subsequently developed tumours. Two breeding females had typical multiple tumours appearing at ages of 64 and 66 weeks respectively. The remaining breeding female and the two virgins had tumours of atypical structure; the tumours in the breeding female and that in one of the virgins developed at or near the point of needle entry for an intraperitoneal injection of an oily solution of a carcinogen and, therefore, were not certainly spontaneous growths.

The BR F_1 hybrids were not bred primarily for the determination of mammary tumour incidence, and the records are unsatisfactory for that purpose. Some mice received intraperitoneal injections of carcinogens whose contribution to the development of mammary tumours was difficult to assess; others were used for transplantation experiments. The mice which survived to tumour age, though not themselves used for experiment, were not certainly representative of the whole colony and, owing to the concentration of tumours in families, the inclusion or omission of a single litter could greatly alter the tumour incidence calculated on the small numbers available. Consequently only a tentative estimate of the mammary tumour incidence is practicable. Of the original colony of 71 breeding females, 11 (15 per cent) developed typical mammary tumours at an average age of 40 weeks (range 26 to 66 weeks); 7 of the mice were "normal." 3 had received intraperitoneal injections of a carcinogen and 1 a tumour implant. Three out of 22 virgins developed tumours. A typical tumour was found at the age of 55 weeks near the site of injection of a carcinogen, 1 atypical tumour at the age of 81 weeks also near the site of injection of a carcinogen, and another atypical tumour at the age of 110 weeks in a "normal" virgin.

The breeding of BR F_1 hybrids was continued, from other parents, mainly to provide hosts for transplantation experiments. Only a minority of mice

survived to tumour age and no estimate of the mammary tumour incidence is possible. Typical mammary tumours developed in 12 breeding females at an average age of 36 weeks (range 26–64 weeks). Seven of the tumour-bearing mice were from three litters containing respectively 3, 2 and 2 tumour-bearing sisters. It was evident that the occurrence of mammary tumours in the earlier series was not fortuitous.

It was concluded that a low or moderate incidence of mammary tumours in BR F_1 hybrids was accountable to a high incidence of mammary tumours in a minority of families, the majority of families being tumour-free. The breeding experiments described in the next section were designed to test the hypothesis that the BR F_1 hybrids were heterogeneous in their capacity for mammary tumour production.

Mammary tumours in the progeny of BR F_1 mice.

Progeny were obtained from 2 tumour-bearing BR F_1 females, BR4 and BR6 (bearers of the tumours CR4 and CR6 recorded in the earlier paper (Foulds,

FIG. 1.—Scheme of breeding from tumour-bearing and tumour-free hybrids.

1947)), and from 1 female, BR16, which had a lung tumour but no discernible mammary tumour when killed at the age of 130 weeks.

Mouse BR6 was mated with a sibling male to provide the F₂ generation in the strain BR6. Mouse BR4 was mated firstly with a brother to start a strain designated BR4 (pink label), and secondly with an unrelated BR F_1 male, No. 1, to start the strain BR4 (blue label). Male No. 1 also sired the tumour-free female to start the strain BR16. Fig. 1 shows the provenance of the four strains. Each strain was continued by brother-sister matings. The F₂ females bred normally and raised their litters. Most of the F₃ females raised one litter and many raised two or three litters; subsequently they were subjected to forced breeding. Selected F₄ females raised one or more litters to continue the strains, but most F₄ females were subjected to forced breeding throughout their reproductive lives. All the mice were similarly housed and fed.

Pedigrees of all mice were kept and the record included a note of the coat colour; the BR F_1 hybrids were all of brown or "wild" colour and their progeny were classified as "wild," "white" or "black," minor variations being ignored. Selective breeding in the F₄ generation established "wild," "white" and

“black” sublines which, with rare exceptions, have bred true to type as far as the F_8 generation.

The results for the first three generations (hybrid generations F_2 – F_4) are given in Tables I–IV. The “effective total” is the number of mice which survived to the age at which the earliest tumour was detected in any of the groups, namely 110 days in an F_4 mouse of strain BR4 (blue label). The “average tumour age” is the average age at which a tumour was first detected, the mice being inspected twice weekly. The mice alive with tumours include mice with nodules growing and regressing in repeated cycles; as described by Foulds (1949b), mice with these nodules almost always die with large typical tumours. Mice in which nodules were present at some period but not at the

TABLE I.—*Strain BR4 (Pink Label).*

Hybrid generation.	Effective total.	Tumour-free.				Tumour-bearing.				Total tumours.	Tumour incidence (%).	Average tumour age (weeks).
		Dead.		Alive.		Dead.		Alive.				
		No.	Average age at death (weeks).	No.	Average age (weeks).	No.	Average age at death (weeks).	No.	Average age (weeks).			
F ₂	4	1	28	0	—	3	62	0	—	3	75	62
F ₃	37	15	34	0	—	22	48	0	—	22	59	36
F ₄	109	19	30	9	69	79	47	2	60	81	74	36

TABLE II.—*Strain BR4 (Blue Label).*

Hybrid generation.	Effective total.	Tumour-free.				Tumour-bearing.				Total tumours.	Tumour incidence (%).	Average tumour age (weeks).
		Dead.		Alive.		Dead.		Alive.				
		No.	Average age at death (weeks).	No.	Average age (weeks).	No.	Average age at death (weeks).	No.	Average age (weeks).			
F ₂	6	2	42	0	—	4	61	0	—	4	67	51
F ₃	52	13	33	4	70	33	59	2	69	35	67	35
F ₄	101	4	38	19	60	69	47	9	65	78	77	35

TABLE III.—*Strain BR6.*

Hybrid generation.	Effective total.	Tumour-free.				Tumour-bearing.				Total tumours.	Tumour incidence (%).	Average tumour age (weeks).
		Dead.		Alive.		Dead.		Alive.				
		No.	Average age at death (weeks).	No.	Average age (weeks).	No.	Average age at death (weeks).	No.	Average age (weeks).			
F ₂	4	2	34	0	—	2	58	0	—	2	50	50
F ₃	34	8	35	1	55	23	53	2	56	25	74	39
F ₄	98	11	30	6	59	75	50	6	58	81	83	35

TABLE IV.—*Strain BR16.*

Hybrid generation.	Effective total.	Tumour-free.				Tumour-bearing.				Total tumours.	Tumour incidence (%).	Average tumour age (weeks).
		Dead.		Alive.		Dead.		Alive.				
		No.	Average age at death (weeks).	No.	Average age (weeks).	No.	Average age at death (weeks).	No.	Average age (weeks).			
F ₂	10	2	54	8	89	0	—	0	—	0	0	—
F ₃	97	14	43	80	66	2	68	1	79	3	3	67
F ₄	136	14	26	120	62	1	54	1	69	2	1	59

time of death are recorded as tumour-free. Many of the mice recorded as dead without tumour succumbed to epidemic infection about a year after the beginning of the experiment.

Tables I-III show that the incidence of tumours in the strains BR4 (pink label), BR4 (blue label), and BR6 was unequivocally "high." The three strains were substantially alike. Tumours developed, indiscriminately as it seemed, in "wild," "white," and "black" mice in the F_2 - F_4 generations and continue to develop in "white" and "black" sublines up to the F_6 generation. The later age-incidence of tumours in the F_2 females was probably attributable to the breeding history; the F_2 females, in contrast with later generations, were not subjected to forced breeding.

The incidence of tumours in the BR16 strain (Table IV) so far is extremely low. The great majority of the mice survive and more tumours may yet develop, but the average age is already higher than the average age of tumour development in the other three strains. Whatever the final incidence, the contrast between strain BR16 and strains BR4 (pink label), BR4 (blue label), and BR6 is unmistakable.

Mammary tumour agent in transplanted BR1 tumours.

Extracts of transplanted tumours of the hormone-dependent BR1 strain (CR1 in the previous report by Foulds (1947)) were injected into female BA F_1 mice (C57 black ♀ × A ♂). According to previous experience in this laboratory (Gye, 1948), BA F_1 hybrids do not develop mammary tumours spontaneously although other laboratories record a low incidence; mammary tumours develop when tumour agent is supplied by foster-nursing or by injection.

The BA F_1 hybrids were 33-46 days old at the beginning of the experiment. Litter mates were allotted as equally as possible to three groups; one group received extracts of BR1 tumours; another group received extracts of spontaneous mammary tumours from mice of high-tumour strains; the third group received no injections. Tumours were ground in a mortar with sand and saline to make suspensions which ranged in strength, in different experiments, from 13 to 20 per cent W/V. The debris was removed by spinning in an ordinary centrifuge, and the supernatant fluid was injected, at weekly intervals, into the dorsal subcutaneous tissues, each dose being 1.0 c.c. Sixteen mice received each 4 injections of extracts of BR1 tumours of the first or third transplanted generations, five received 3 injections and two received 2 injections. Twelve mice received each 1 injection of an extract of a primary spontaneous C_3H tumour and 3 injections of primary spontaneous R3 tumours, and seven mice received 3 injections of the R3 extracts only. All the extracts were similarly prepared. The females were caged with males and subjected to forced breeding, litters being removed within 48 hours (usually within 24 hours) of birth.

Table V summarizes the results at 89 weeks from the beginning of the experiment. The "effective totals" comprise the mice which survived to the age when the first tumour was detected (180 days in a mouse injected with BR1 extract). Tumours developed with comparable frequency in the two groups which received tumour extracts and at similar times; none developed, within the period of observation, in the control mice, 11 of which survived, without apparent tumours at ages of 92-96 weeks. The extracts were not certainly free from living

cells, but the possibility that the tumours resulted from cell transplantation was negligible, being discounted by the development of tumours in mammary tissue at sites remote from the point of injection, by the long intervals between the injections and the appearance of tumours, and by the genetic differences between the mice providing the extracts and the mice which developed tumours.

TABLE V.—*Tumour Incidence in Injected and Normal BA F₁ Mice.*

Experiment.	Effective total.	Dead without tumour.		Alive without tumour.		Dead with tumour.	
		No.	Average age (weeks).	No.	Average age (weeks).	No.	Average tumour age (weeks).
BR1 tumour extract . . .	21	2	55	0	—	19	48
Spontaneous tumour extract	17	3	66	0	—	(90.5%) 14	43
Normal controls . . .	12	1	82	11	94	(82.4%) 0	—

The results indicated that transplanted BR1 tumours contained mammary tumour agent comparable in activity with that in spontaneous growths in high mammary tumour strains.

Spontaneous mammary tumours in RB F₁ mice.

A colony of RB F₁ mice (R3 ♀ × C57 black ♂) was maintained to compare the tumour incidence with that in BR F₁ hybrids. The mice were subjected to forced breeding like the BR mice and similarly housed and fed. Of the effective total of 36 females, 33 (91.7 per cent) developed mammary tumours. The average number of tumours per mouse was 2.5, 24 mice having from 2 to 6 tumours each. The average age at the first detection of a tumour was 25 weeks; the earliest tumour was recorded at the age of 17 weeks, and the latest at 54 weeks.

The 3 mice without tumours are alive at ages of 81, 81 and 85 weeks respectively. It is noteworthy that although continuously with males they have had no litters for about a year; previously litters were not recorded. No observations were made on virgin mice.

Incidence of tumours in (C57 black ♀ × agent-free R3 ♂) F₁ hybrids.

Female mice taken at random from the laboratory stock of C57 black were mated with males from a colony of R3 mice free from milk agent. I am indebted for the male mice to my colleague Dr. B. D. Pullinger, who raised the colony from a litter of R3 mice removed from their mothers immediately after birth and suckled by C57 black foster-mothers. Up to the present only 2 atypical mammary tumours, of squamous type, have developed at the age of 23 months amongst 117 breeding females over 9 months old (Pullinger, 1947, and personal communication). The F₁ hybrids were subjected to forced breeding throughout their reproductive lives.

One hundred female hybrids were reared; 21 died without tumours at an average age of 21 weeks and 79 are alive at an average age of 57 weeks. Of the surviving mice, 29 are less than a year old (average 39 weeks) and 50 are over a year old (average 67 weeks). The only tumour encountered so far was detected at the age of 64 weeks in a mouse which survives; the structure of the tumour

is unknown. Up to the present therefore the incidence in mice over a year old is 2 per cent.

Of the 23 tumours found in BR F_1 hybrids with normal R3 fathers, 20 were first seen in mice less than a year old, the average age at detection being 38 weeks. The incidence in BR F_1 hybrids with agent-free R3 fathers is much lower or much later.

Table VI summarizes for easy comparison the incidences of mammary tumours in the various hybrids.

TABLE VI.—*Summary of Tumour Incidences.*

		Effective total.	Tumour incidence (%).	Average tumour age (weeks).
BR F_1		71	15	40
BR F_1 (Agent-free ♂)		50	2	64
RB F_1		36	92	25
Strain BR4 (pink label)	} $\begin{cases} F_2 \\ F_3 \\ F_4 \end{cases}$	14	64	55
„ BR4 (blue „)		123	67	39
„ BR6		308	77	35
Strain BR16	} $\begin{cases} F_2 \\ F_3 \\ F_4 \end{cases}$	10	0	—
		97	3	67
		136	1	59

DISCUSSION.

Andervont (1945*a*) reviewed the records of relatively high incidence of mammary tumours in hybrid mice having low-tumour strain mothers, and hence presumed deficient in the mammary tumour agent. The possible explanations of the phenomenon were speculative because tests for the presence of tumour agent in the hybrids were not made. Subsequently, Andervont (1945*b*) and Andervont and Dunn (1948, *a*, *b*, *c*) investigated the occurrence of tumours in mice with strain C (low-tumour) mothers and strain C3H (high-tumour) fathers. Their results, which corresponded in some respects with my observations on hybrids with C57 black (low-tumour) mothers and R3 (high-tumour) fathers but differed in other respects, are discussed in later paragraphs.

The incidence of tumours in BR F_1 hybrids (C57 black ♀ × R3 ♂) resembled that recorded by others for various hybrids with low-tumour strain mothers and high-tumour strain fathers. Although the incidence was not high the tumours appeared at an average age of 38 weeks, which was within the range of age incidences of tumours in high-tumour strains. The histological structure was unremarkable except in two tumours which developed near the sites of injection of a carcinogen and in one tumour in a virgin. The sex-limited transplantation described in a previous paper was not peculiar to BR F_1 hybrids; as recorded in the paper which follows (Foulds, 1949*a*), some tumours in the reciprocal RB F_1 hybrids, which had a high incidence of tumours, behaved similarly. Mammary tumour agent, comparable in activity with the agent present in spontaneous tumours of high-tumour strain mice, was demonstrated in a transplanted BR F_1 tumour. The BR F_1 tumours, therefore, differed consistently in no particular from the typical mammary tumours of mice of inbred high-tumour strains. The tumours, however, were concentrated in a minority of litters of BR F_1 mice, the majority of families having none so that the total incidence was relatively low. Observations on the F_2 and subsequent

generations confirmed the implication that the BR F_1 hybrids were heterogeneous.

The descendants of the two tumour-bearing BR F_1 females had a high incidence of tumours at a relatively early age, and resembled in all respects mice of inbred high-tumour strains. The high incidence was maintained at least to the F_5 or F_6 generations. The diversity of genetic constitution in the F_2 and subsequent generations did not noticeably affect the incidence of tumours which developed indiscriminately in "black," "white" and "wild" mice and in each of the "black," "white" and "wild" sublimes established by selective breeding. By contrast the tumour incidence in the progeny of a tumour-free BR F_1 female sired by a male that sired, also, one of the high tumour strains was extremely low or extremely late. These results recalled Bittner's (1940) observations on strain A mice nursed by C57 black foster-mothers. A minority (7.9 per cent) of the fostered A females developed mammary tumours, presumably because they received tumour agent from their strain A mothers before being transferred to foster-mothers, and the tumour incidence in their progeny was high (58.5 per cent). The majority of the fostered A mice developed no tumours and the incidence in their progeny was low (6.1 per cent).

In sum, the observations indicated that a minority of (C57 black $\text{♀} \times \text{R3 } \text{♂}$) F_1 hybrid females carried and transmitted the mammary tumour agent and developed mammary tumours, whereas the majority of the mice did not carry or transmit the agent and did not develop tumours. Direct and indirect evidence for the presence of tumour agent in tumour-bearing hybrids limits discussion to the source of the agent and the reason for its uneven distribution amongst the F_1 hybrids.

The sublimes of C57 black mice maintained in various laboratories are not now identical and some possibly carry the mammary tumour agent, perhaps in attenuated or masked form. In this laboratory mammary tumours have not been recorded in the pedigreed stock although they have occurred, rarely, in unpedigreed mice derived from the C57 black stock as, for example, by random interbreeding; our subline maintains therefore the essential characteristics of the original stock. Mammary tumours have developed in two types of hybrid with C57 black mothers, namely (C57 black $\times \text{R3}$) F_1 and (C57 black $\times \text{C3H}$) F_1 but not in a third type (C57 black $\times \text{A}$) F_1 (Gye, 1948, and this paper). Evidently the strain of the father had a substantial effect on the incidence of tumours in F_1 hybrids. The paternal contribution was not probably genetic for, as shown in this paper and in previous reports from this laboratory (Dmochowski, 1944, 1945), the C57 black $\times \text{A}$ hybrids developed tumours abundantly when tumour agent was supplied to them artificially. The uncompleted observations on hybrids having fathers belonging to a subline of R3 mice deprived of tumour agent accorded with similar observations by Andervont and Dunn (1948*a*, *b*, *c*) in showing a substantial reduction in the incidence of tumours in comparison with similar hybrids whose fathers derived from a line carrying the tumour agent. The experiment was open to the criticism, which Andervont and Dunn applied to their own experiment, that the agent-free and agent-bearing males were separated by several generations of inbreeding and possibly differed genetically. With this reservation, both experiments indicated a transmission of tumour agent by males of high-tumour strains to their hybrid offspring. The probability of this interpretation was increased by Andervont

develop early tumours exactly comparable with the BR F_1 tumours, but tumours develop in a high proportion of the remaining mice about a year later. The late tumours in which tumour agent has not been demonstrated account for the exceptionally high tumour-incidence in these particular hybrids. The present investigations provide no clue to the nature of the late tumours. It is evident, however, that the ($C \times C3H$) F_1 hybrids, like the BR F_1 hybrids, are heterogeneous.

It is noteworthy that experimental deprivation of tumour agent greatly reduces but does not completely suppress the development of mammary tumours. My observations add two examples, namely the line BR16 established by breeding from a tumour-free hybrid female, and the colony of F_1 hybrids derived from C57 black females and R3 males deprived of milk agent. The aetiology of these "residual" tumours, which possibly correspond with the late tumours in ($C \times C3H$) F_1 hybrids, is obscure.

SUMMARY.

Typical mammary tumours developed in about 15 per cent of the breeding females of the first generation hybrids, C57 black $\text{♀} \times$ R3 ♂ at an average age of 40 weeks. The incidence of tumours in the reciprocal hybrids, R3 $\text{♀} \times$ C57 black ♂ , was 92 per cent at an average age of 25 weeks.

Mammary tumour agent was demonstrated in a transplantable tumour which originated in a (C57 black $\text{♀} \times$ R3 ♂) F_1 mouse by injecting tumour extracts into (C57 black $\text{♀} \times$ A ♂) F_1 hybrids which, otherwise, did not develop mammary tumours. The progeny of two tumour-bearing (C57 black $\text{♀} \times$ R3 ♂) F_1 females had a high incidence of mammary tumours (about 70 per cent) maintained through at least 5 generations. By contrast the progeny of a tumour-free female had a low incidence (0–3 per cent) similarly maintained. It was concluded that the F_1 hybrids were heterogeneous; a minority, concentrated in certain litters, developed mammary tumours, carried the mammary tumour agent and transmitted the agent to their offspring, which had a high incidence of tumours; the majority did not develop tumours and did not transmit the tumour agent to their offspring, which, with rare exceptions, did not develop tumours. Since the incidence in (C57 black $\text{♀} \times$ R3 ♂) F_1 hybrids was reduced or delayed when the male parent derived from a line of R3 freed from tumour agent, the low or moderate incidence of mammary tumours in hybrid mice with low-tumour strain mothers and high-tumour strain fathers was attributed, provisionally, to the erratic transmission of tumour agent by the male parents.

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