## Title

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## DISCLAIMER

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# Development of Spontaneous Mammary Tumors over the Life Span of the Female Sprague-Dawley Rat: The Influence of Ovariectomy, Thyroidectomy, and Adrenalectomy-Ovariectomy[1]

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## SUMMARY

Several groups of virgin female "COBS" (Cesarean-Originated, Barrier-Sustained) Sprague-Dawley rats were observed for the incidence of mammary tumors (MT) over their entire life span. Maximum life span varied from 885 to 1040 days. Crude MT incidence for all groups was 61.7%. When the life table method was used to correct for extraneous deaths, the mean value for all groups was 71.5 ± 5.7% MT bearers. The age at onset of the median MT was 671 ± 41 days. Curves of cumulative MT incidence indicated close agreement among control groups early and late in life, with the greatest variability appearing from the 500th to the 850th day of age.

Examination of MT development rates indicated that there were at least three age-related changes in normally ageing rats--two leading to abrupt increases in the rate of development of MT occurring at about the 500th and the 660th day of life, and a third change late in life, after the 800th day, leading to a decrease in MT morbidity rate.

Neither MT incidence or incidence rate of uniparous rats were different from virgin controls. Thyroidectomy did not reduce the life-span incidence of MT, but did postpone slightly those MT arising late in life. Ovariectomy nearly eliminated MT development; only 6.7% of OX rats developed MT over a maximum life span of 1295 days. Removal of both ovaries and adrenals

completely eliminated MT. ADX-OX rats lived long enough (maximum life span 1110 days) to have permitted observation of late-appearing MT.

The proportion of MT that were diagnosed as carcinomas in the control groups was highly variable, 18.6 ± 12.1%. Carcinomas in these studies did not appear to arise sooner than benign fibroadenomata. Other superficial tumors arising in tissues different from the breast are tabulated.

The results of these studies are compared with those from other laboratories. The possible relationships between development of spontaneous MT and the age-related changes in the ovary and pituitary gland are briefly discussed.

# INTRODUCTION

Mammary tumors (MT) of the rat have been studied for more than 60 years (1-3). Noble and Cutts (4) and Clifton (5) recently reviewed the general field of murine breast tumors, their artificial induction, and their dependence on hormonal status.

MT occur spontaneously in old rats (4). They can also be readily induced in young females by various means -- (a) by external application (6, 7), feeding (8, 9), or injection (10) of aromatic amines (11) or aromatic polynuclear hydrocarbons (6-10); (b) by injection (12) or implantation of estrogen (13); and (c) by several forms of ionizing radiation--single exposures of x-rays (14-17), $\gamma$-rays (18), and proton beams (19); multiple exposures of $\gamma$-rays (20) or neutrons (20, 21); and by internal irradiation with the $\alpha$-particle emitter, $At^{211}$ (22).

Histologically, both benign and malignant MT occur spontaneously, the majority being benign fibroadenomata (4). The proportions of malignant and benign MT induced by radiation are similar to those encountered with spontaneous MT (14). When the inducing agent is estrogen or a hydrocarbon, the proportion of malignancies is definitely increased (9, 13).

MT of the rat are highly sensitive to hormone manipulation. Ovariectomy drastically reduces (23-25) and hyphysectomy abolishes (24-25) MT development stimulated either by hydrocarbons or radiation in females, and neither inducing agent is particularly effective in inducing MT in intact males (26, 27). Established MT frequently regress when the ovaries are removed (28) or the estrogen supplement is withdrawn (13); and implants of fibroadenomata take poorly in ovariectomized females or in male hosts (29). The adrenals have also been implicated in MT induction as a possible source of estrogenic hormones in gonadectomized animals (12, 25).

While there appear to be differences among strains, significant numbers of MT arise spontaneously in ageing rats of most strains (20, 30-40). The

similarity of the chronic effects of radiation and the physiological changes accompanying natural ageing (of which MT development is one manifestation) led Bond et al. (41) to comment:

"When neoplasms of the types under study (i. e. mammary tumors) increase in time in control animals, the question arises as to whether the radiation is inducing a process, or merely accelerating a process that would normally occur in time. This question is difficult, if not impossible, to answer satisfactorily since a meaningful value for the 'normal' incidence is difficult to obtain. In general, the likelihood of neoplasia increases with age, and it is not possible to state whether neoplasia of a given type would have appeared in decedents."

Determination of a meaningful value for the life-span incidence of MT in a normal rat population is indeed difficult, inasmuch as the life expectancy in most rat colonies is less than 2 years. Except in one instance when heroic measures were taken to reduce pulmonary infections (35), MT and other lesions common to the latter half of the life span were obscured by a high mortality from infectious diseases. Investigation of MT induction by radiation or other carcinogens was severely hampered by lack of information on MT incidence in ageing controls (18). Thorough study of the MT incidence, and its age distribution over the life span of the Sprague-Dawley rat (one of the most MT-susceptible strains, and one of the strains most prone to succumb early from lung disease), was possible only when "COBS" (Cesarean-Originated, Barrier-Sustained) rats became available in large quantities.

This report covers a 6-year study of the incidence of spontaneous MT in a colony of female Sprague-Dawley rats whose maximum life span was close to 3 years. We have determined the total MT incidence and the age-specific incidence of spontaneous MT and the variability of both among different shipments from the same supplier. Effect on spontaneous MT incidence

of removal of the ovaries, adrenals, or thyroid glands was also investigated. The proportions of benign and malignant tumors and their variability, and the occurrence of superficial tumors originating from tissues other than the breast, are briefly discussed.

## METHODS AND MATERIALS

Animals and Animal Care. --The rats used in these studies were "COBS" females of the Sprague-Dawley strain purchased over a 4-year period from the Charles River Breeding Laboratories, North Wilmington, Massachusetts. The number of rats in each shipment, their birth date, and any special treatment are shown in Table 1.

Rats were received as weanlings, except for the uniparous group (UP, lot 15). On arrival they were earmarked and caged in groups of five. As the animals grew larger they were redistributed so that the largest rats were caged in pairs. The cages were made of plastic with stainless steel tops. A layer of sterilized wood shavings served as bedding. Cages were changed, washed, and sterilized twice a week. Purina Lab Chow and tap water were fed ad lib. The adrenolectomized-ovariectomized rats were maintained on isotonic saline.

Just before receipt of the first shipments of "COBS" rats the stockroom was cleared of rats; the premises were completely cleaned and fumigated; and all movable equipment was sterilized. During these studies only "COBS" rats were kept in the colony. Deaths from pulmonary and other infections were rare, indicating that an essentially disease-free colony was being maintained with the minimal procedures described above.

All rats in the colony were weighed and examined once a month. The individual record of each rat included the monthly weight, the date a MT was first observed, its approximate location and notes on its subsequent growth, and comments on general health. Since the goal of the experiment was to keep

a rat healthy until a MT developed, rats with simple debilitating conditions were specially treated. Rats with vaginal bleeding or skin sores were isolated to prevent cannibalism. Skin lesions were painted with gentian violet or zephiran chloride. If the bleeding stopped or the skin sores healed, the rat was returned to the colony. If the animal continued to deteriorate, it was sacrificed. Rats with spread or broken incisors were caged separately and given powdered food. The overgrown opposite teeth were clipped periodically to facilitate eating and to prevent laceration of the jaw.

Cages were examined daily for sick or dead rats. Dead rats were examined to determine cause of death, if possible. Moribund rats and those that had bloody encrustations around the eyes and nose and had been losing weight rapidly were sacrificed. This combination of symptoms usually indicated a large pituitary tumor or a pulmonary infection.

There were only two end points considered in this study--development of the first MT (referred to as the primary MT) or death without a MT. Once a rat had developed one MT, it was a statistic. However, MT bearers were usually sacrificed in groups for convenience, and several months often elapsed between observation of the primary MT and death of the animal. Unless a MT was already large when it was first seen, the animal was held for additional observation to make sure the palpable lump was an established MT and not just hyperplastic mammary tissue or subcutaneous fat. The $Sr^{85}$- or $Ca^{45}$-injected rats[3] were primarily part of other experiments, for which it was necessary to keep them alive as long as possible, or in the $Ca^{45}$ group, at least until the next regularly scheduled sacrifice. When one of these rats developed a MT, it was resected, and the animal was returned to the primary experiment. The The resected MT was weighed, given an experimental number, and prepared for histology.

At autopsy or sacrifice the animals were examined, and the gross findings were recorded. Tumors of all kinds, endocrine glands including the pituitary, and samples of other tissues and organs were weighed and fixed for histology. The results of the collateral studies will be reported elsewhere.

Because of the lapse of time between the first observation of a MT and sacrifice of the rat, some other superficial tumors occasionally developed. When more than one superificial tumor was found at autopsy and there was no record of the location of the primary MT, the heaviest was designated as primary. In a few instances, although rats were sacrificed as MT bearers, histological examination of the tumor indicated an origin from a different tissue. If this were the only tumor present, the rat was removed from the MT group and recorded as having died without a MT. If a proven MT was also present, the largest was designated as the primary MT.

The individual animal records were transferred to punched cards for handling. Each data card contained the following information: lot number, experimental group, animal number, histology reference number, age at death, weight and diagnosis of the primary MT, weight and pathological diagnosis of the pituitary, diagnosis of other superficial tumors if any, age when the primary MT was first observed, age at MT resection when applicable, age at onset of the primary MT ($T_a$, calculated as described below), and a notation if death without a MT was classified as extraneous, i.e., accidental, deliberate sacrifice, or proven pulmonary infection.

Undiagnosed MT--All but a few MT were diagnosed microscopically. In 14 cases MT bearers died without autopsy and were inadvertently destroyed or the tumorous area had been eaten by cage mates. In 15 other cases MT specimens were lost during histological preparation. The total number of primary MT observed was 335, of which this group of 29 represented 8.6%.

As discussed at the end of the section on Results, the chances were less than one in 25 that these undiagnosed superficial tumors had not originated from the breast. It was therefore assumed that such tumors were most probably MT, and further that they were probably benign fibroadenomata (FA).[4]

Determination of the age at onset of MT. --The basic end points of this study were age at death for those animals dying without a MT, or the age at onset of the first MT. Age at death was an integral part of the record for each rat. Age at MT onset was more difficult to establish. Pressure of work in the laboratory restricted examination for tumors to once a month. During the 6-year course of the study many people were involved in the examinations. Weighing and palpating a large, colony, even once a month, was sufficiently time-consuming that examinations were often hasty; and the examinations conducted by inexperienced personnel were often inadequate. As a result, some MT were first detected when barely palpable, but the majority were not seen until they had grown quite large.

Because of this disparity in size when the MT were first observed, it was necessary to develop a method of normalizing the age at MT onset. The method chosen was construction of a growth curve as shown in Chart 1 for the "average" FA, the most common rat breast tumor. The construction of the curve, and the errors involved in its use, are described elsewhere (42).

The MT size chosen as the reference for MT onset was 1 cm diameter, or--assuming unit density for tumor tissue--a weight of 0.5 gm. The age at onset, $T_a$, was thus defined as the age of the animal when its first MT was reference size. The weight of the MT at autopsy or resection was entered into the curve in Chart 1 to determine the growth interval (GI), the number of days the MT had been growing since it weighed 0.5 gm. $T_a$ was then obtained from the relation

$T_a$ = (age at autopsy or resection)-- (growth interval ± S. E. ).

The standard error of estimate of the growth curve (reference 46, Chapter 16), shown as the shaded area in the Chart, was small enough so that the uncertainty in $T_a$ was never more than 30 days. The growth rates of a small sample of mammary carcinomas (CA) were compared to the growth of FA (42). No difference in growth rates was detectable. The age at onset of MT diagnosed as CA was therefore also estimated from Chart 1. As will be shown in the section on results, the distributions of age at onset of FA and CA were alike and no distinction was made in the analysis that follows between MT diagnosed as malignant or benign.

Preparation of life tables--The data cards for each control and experimental group were sorted into MT bearers and rats dying without MT. MT bearers were arranged in order of increasing age at onset of the primary MT as calculated from the growth curve. Rats dying without MT were arranged in order of increasing age at death. Rats without MT were further divided into two groups--those whose deaths were considered extraneous and those that died of causes related to or possibly related to natural ageing. The life tables of all groups are collected in the Appendix.

Separate life tables were prepared for the $Ca^{45}$ group and for lot I, the undisturbed portion of the first shipment. These two parts of the same basic group were examined separately to determine the ability of actuarial methods to correct for the substantial early losses of rats demanded by the predetermined sacrifice schedule of the $Ca^{45}$ study. Lot 14, which was essentially undisturbed, was divided for analytical purposes into two groups at the central rat number. A separate life table was prepared for each half, 14-1 and 14-2; these were to serve as controls for the separately maintained portions of lot 1, and also to examine how closely part of a group represented the behavior of the whole group.

Actuarial correction for extraneous deaths--The actuarial interval used throughout this analysis was 30 days. Use of a longer interval would have obscured some age-dependent phenomena.

The method used to correct for deaths known to be unrelated to ageing (column 4 in the life tables) was that described by Berkson and Gage (43). This correction assumes that rats dying during the 30-day interval are, on the average, under observation for half the interval; they are thereafter eliminated from the population at risk. Pilgrim and Dowd (44) recently pointed out some errors in this method, and have devised a more precise way of taking extraneous deaths into account. However, the correction used in this report was considered adequate for the following reasons; (a) The number of extraneous deaths, i.e., those entirely unrelated to ageing, was relatively small; (b) many of the rats that died without a MT succumbed to pituitary tumors, and these have been shown to be intimately related to MT development (5, 45); (c) we wished to describe MT morbidity in the presence of other lesions and diseases associated with ageing rather than MT morbidity as an independent entity.

## RESULTS

MT incidence over the life span of the normally ageing female rat--The crude MT incidence--i.e., the proportion of the starting population that eventually developed one MT--and the actuarially corrected MT incidence are shown in Table 2 for the various control and experimental groups. There were no extraneous deaths in lot 12, or the TX or OX groups; therefore, the crude MT incidences of these groups are the same as the corrected values. Actuarial correction substantially reduced the spread among the virgin control groups; MT incidence over the life span (1020 days) of four groups of "COBS" rats obtained from the Charles River Laboratories (lots 1, 11, 12, and 14 combined) was 71.5 ± 5.7%.

The maximum life spans of the control groups varied from 885 to 1010 days, therefore, the MT incidence at 900 days--an age late in life that was attained by all the groups--is also shown in Table 2. The MT incidence at 660 days is included so that the early behavior of lot 17 (23 of these rats are still alive at this writing) may be compared with the other control groups.

Table 3 shows some of the gross features of the age dependence of MT development in the normally ageing female rat: the age at onset of the first MT in the group; the age at which 25% of the group's MT had developed (25th percentile); the age at onset of the median MT; the age at which 75% of the group's MT had developed (75th percentile); and the age at onset of the last MT in the group. Among the virgin control groups there was a range of nearly 200 days in the age at onset of the first MT. The span of age at development of the median MT was narrower, 120 days, as was the age span when the last MT appeared, 125 days. The average value for the age of a control group at the onset of the median MT was 671 ± 41 days, and for development of the last MT, 945 ± 41 days.

Cumulative MT incidence--The life span MT incidences of the five virgin control groups obtained from the Charles River Laboratories (lots I, 11, 12, 14, and 17) are shown in Chart 2 as standard linear plots of cumulative MT incidence vs. age. The shapes of the curves were similar at the younger ages, and they tended to converge to a common value late in life. However, there was somewhat greater variation in the curve shapes from the 500th to the 850th day of age. Furth and others (5, 45) have suggested that MT in rodents arise as the result of complex interactions of the ovary, adrenal glands, and pituitary. It might be expected that these interactions are initiated and continue to act over a span of time rather than at some precise age. If the stimuli that are presumed to initiate MT have a variable span at onset and action, then the time at onset of

MT should also display a certain amount of variation over the same age range. Tables 2 and 3 and Chart 2 indicate that the most reliable characterizations of the total ultimate MT incidence of a rat population are the median age at onset and the percentage incidence over the life span.

The cumulative MT incidence of the $Ca^{45}$ group from which healthy non-tumorous rats were deliberately sacrificed to meet a predetermined schedule is compared with their undisturbed control group (lot I) in Chart 3. The curves coincided until the 700th day and diverged thereafter. This divergence was statistically significant after the 750th day (the $\chi^2$ test for goodness of fit (46) yielded a P value of 0.01). In contrast, the cumulative MT incidence curves (not shown) of the two parts of lot 14 were nearly identical. It was concluded that the early loss of close to 30% of the starting population had so altered the behavior of the $Ca^{45}$ group that even actuarial corrections were grossly inadequate. The $Ca^{45}$ group was therefore not included in the combined virgin control group.

Effect of uniparity, thyroidectomy, ovariectomy, or adrenalectomy-ovariectomy on life span MT incidence--It is apparent from Table 2 that neither uniparity or thyroid deficiency influenced the percentage of rats that eventually developed MT. Examination of the quartile distribution of age at MT onset in Table 3 indicated that uniparous rats not only developed the same percentage of MT over the life span, but also developed them at the same ages as virgin animals. Table 3 and Chart 4 indicated that while thyroid deficiency from the 84th day of life did not change the total life span MT incidence, there was some difference in the age distribution of the tumors. From the 600th to the 850th day of life the TX group was developing fewer MT than the intact controls. Thyroid deficiency evidently delayed MT development during this period and in so doing prolonged the life of the animals by about 200 days.

As expected, ovariectomy (at 77 days of age) nearly eliminated MT. Only

three MT containing epithelial components were found in the 45 OX rats. Appearance of the first MT in the OX group was 200 days later than the first MT found in lot A, the control group in which MT developed most slowly. The OX rats were very long-lived; the maximum life span of the group was 1295 days, nearly 25% longer than intact controls, and more than half of the group lived longer than 1000 days. The life span of a sufficiently large proportion of this group was certainly long enough to have permitted observation of late-appearing MT, if the effect of ovariectomy had postponed development rather than prevention.

Removal of both the adrenal glands and the ovaries on or before the 110th day of life completely abolished MT of epthelial origin. Both the median and maximum life span of this group were substantially greater than intact controls, as shown in Table 3. The maximum life span was 1110 days, and 29% of these rats lived more than 1000 days. Simple postponement of MT seems unlikely.

Relationship of MT development to age--The data in Table 3 and the curves of percent cumulative MT incidence in Charts 2 and 4 bear out the oft-repeated statement that MT occur most commonly in older rats (4). One of the aims of this study was to examine in detail the relationship between the age of the rat and the development of spontaneous MT Pilgrim and Dowd (44, 47) have described a simple conversion of cumulative incidence data which permits determination of the rate at which a colony is developing a specific lesion, in this case MT.

Percent survival without MT is calculated from the relation

$$\% \text{ survival without MT} = (100 - \% \text{ cumulative MT}).$$

The properties of the curves obtained by plotting % survival without a MT, semilogarithmically, as a function of age have been described by Pilgrim and

Dowd as follows: (a) Similarities or differences in tumor morbidity are often revealed that were not apparent either from life tables or curves of cumulative incidence; (b) any straight-line portion indicates a constant rate of tumor morbidity over that portion; (c) curves that are concave upward indicate a rate of tumor morbidity that decreases with age; (d) curves that are concave downward indicate a rate of tumor moribidity that increases with age; (e) curves are parallel when the only effect is to delay the age at onset; (f) sharp changes in slope indicate age-dependent changes in the population; (g) the logarithm of the slope of the survival curve plotted as a function of age is the familiar Gompertz curve of force of mortality.

Survival curves for five control groups are shown in Chart 5. The actual data points are not given; however, the straight lines shown fitted closely to the best smooth curves that could be drawn through the points. The survival curves of four of the five control groups (lot 12 was exceptional) had several common features: (a) During the period from 300 to 500 days of age MT were appearing slowly at an average rate of 1.8% per month; (b) between the 480th and 520th day the rate of MT development increased sharply to 4.3% per month; (c) a second increase in MT development rate to 9.5% per month occurred between the 630th and 690th day; (d) after the 800th day the rate of MT development decreased to 4% per month or less.

There were then at least three age-related changes in these rats, -- two leading to abrupt increases in the rate of development of MT and one late in life leading to a decrease in the rate of MT morbidity.

In Chart 6 the percent survival without MT of the uniparous (UP), thyroidectomized (TX), and outbred control group (lot A) are compared with the survival of the combined Charles River controls. The general shapes of the four curves are similar. The displacements of the inflection points of the UP and lot A curves from the combined control curve were not significant. Both

major inflection points (occurring at 500 and 630 days in the controls) were delayed 100 days in the TX rats, suggesting that thyroid deficiency delayed MT onset by delaying the process or processes responsible for initiating MT.

Probability of developing MT as a function of age--The age-specific MT incidence rate is shown in column 10 of the Life Tables in the Appendix in units of percent MT per rat at risk per month. For this calculation MT bearers were removed from the population at the end of the interval in which their MT developed. All rats dying without MT (columns 2 and 3 of the Life Tables) were removed from the population halfway through the interval in which they died or were lost to follow-up. It can be seen from these Tables that even in groups as large as 120 rats (lot 14, and lot I and $Ca^{45}$ combined) there were 30-day intervals in which no new MT arose, leading to discontinuities in the MT development rate. A modification due to Spicer (48) of the rate of MT development $\mu(x)$ was used to approximate the absolute rate of MT development. By virtue of an averaging and distributing process the function $\mu(x)$ has the properties of reducing fluctuations and eliminating some discontinuities. $\mu(x)$ at any interval, $T_i$ is calculated from

$$\mu(x) = \frac{MT_i + MT_{(i-1)}}{2(N_i)},$$

where $MT_i$ and $MT_{(i-1)}$ are the numbers of MT developing in the intervals $T_i$ and the previous interval, $T_{(i-1)}$, and $N_i$ is the population surviving $T_i$ days without a MT.

The curves of $\mu(x)$ plotted semilogarithmically as functions of age are shown in Chart 7 for the larger individual control groups (lots 1, 14, and 17) and for the combined Charles River virgin controls. The sharp changes in rate of MT development that were noted in the survival curves in Charts 5 and 6 were also detectable as inflection points in all four of the $\mu(x)$ curves in Chart 7.

Simms (49) has pointed out that because of the intimate relation to age of cancer of the sex organs and accessory structures, morbidity curves for these tumors should not be straight lines, but should show irregularities. Because they were composed of a series of nearly straight-line segments over which the slopes [equivalent to $\mu(x)$] were constant, the survival curves on Charts 5 and 6 suggested that a plot of $\mu(x)$ should be discontinuous. After the 300th day, the $\mu(x)$ curves could indeed be interpreted as rising in a stepwise manner rather than increasing continuously.

Incidence of superficial tumors - other than breast tumors--In addition to the primary MT, some animals developed other breast tumors, or tumors of other tissues. Some rats came to autopsy with only tumors of nonbreast origin. The tumors of tissues remote from the breast will be discussed in a later report. Superficial tumors of skin or subcutaneous tissues, unrelated or only questionably related to breast, will be dealt with here.

For the purposes of this study only those tumors diagnosed as adenoma and fibroadenoma (FA) or mammary carcinoma (CA) were considered to have originated (unquestionably) from the breast. Other authors have included fibrosarcoma and fibroma (4, 30) as breast tumors. However, we have chosen only to include as MT those tumors, arising near the mammary line, that contained some epithelial components. The superficial tumors arising in tissues other than breast and those tumors whose mammary origin was questionable are shown in Table 4.

There were 335 MT bearers among the intact rats, 495 virgin females and 53 uniparous animals, yielding an overall raw MT incidence of 61.1%. Of the 30 untreated rats that developed other superficial tumors 15 died without also developing MT. In the absence of histologic confirmation, inclusion of these 15 rats in the MT group would have introduced a small error -- 2.8% (63.9% vs. 61.1%). It was therefore considered reasonable to include those normal

control animals that bore only one superficial tumor as MT bearers, even though the tumor was not diagnosed. However, in two of the smaller experimental groups -- ovariectomized (OX), adrenalectomized-ovariectomized (ADX-OX), -- inclusion of all superficial tumors as MT without histological confirmation would have substantially changed the overall MT incidence. Fortunately, all superficial tumors in these latter groups were diagnosed.

Incidence of Carcinoma--The total numbers of carcinomas (CA) and FA with carcinomatous pockets (CA in situ) that were observed among MT bearers in all groups are shown in Table 5. All but four of the CA were primary MT, i.e., the first MT observed in the rat. The percent of MT bearers whose primary MT was a carcinoma was highly variable within the individual control groups. In the normal virgin control groups the percentage of CA ranged from none (lot A, born in this Laboratory) to a high of 37.5% (lot 17). The overall proportion of CA encountered among the 242 MT-bearing virgin rats born at the Charles River Laboratories was $18.6 \pm 12.1\%$. The variability of CA among normal control groups indicates that all but the most dramatic shifts in proportions of benign and malignant MT should be viewed with skepticism. Small changes are obscured by normal fluctuations, and failure to account for normal fluctuations can lead to ridiculous conclusions. The experimental groups were compared with their nearest controls -- TX with lot 1, and UP with lots 14 and 17 by use of the $\chi^2$ test (47). Neither uniparity nor absence of thyroid hormone appeared to influence the proportion of CA developed. The apparent difference in the proportion of CA between the virgin controls born several years ago and those rats obtained more recently suggests that the breeding practices of the dealer may not be achieving their stated goal of random breeding.

Huggins et al. (50) and Cutts and Noble (13) have shown that when MT are induced by either hydrocarbon feeding or implantation of estrogen pellets,

respectively, CA arise sooner after treatment than do FA. Our data were examined for any indications of the earlier onset of spontaneous CA. The punched data cards of all MT bearers, except those in the TX and OX groups, were sorted according to histological diagnosis. The FA and CA groups were further subdivided by age at MT onset into succeeding 60-day intervals to obtain a frequency distribution. Because of the small number of CA--55 CA compared with 257 FA--the frequencies of MT per interval were converted into percentages of the total number of each kind of tumor. Chart 8 showed that the frequency distributions of FA and CA with age were similar. The median age at onset was nearly identical, 650 days for FA and 675 days for CA. The age span during which the central half of either malignant MT or benign MT occur also coincided. Of the four MT whose age at onset was less than 300 days, only one was a CA. It appeared that there was no difference between age at onset of CA and FA. Combination of all MT into a single population for tumor morbidity analysis was therefore a valid procedure.

## DISCUSSION

It was of interest to compare the results of this study with the MT incidences observed for the female Sprague-Dawley rat in other laboratories. The data available from the literature are shown in Chart 9 along with the curves for our combined Charles River controls and the outbred control group born at LRL (lot A). Single MT incidence values were given by three authors: Davis et al. (34) obtained a MT incidence of 54.8% in a colony whose maximum life span was 1100 days; their observed value is shown as a single point at 1000 days. Thompson et al. (38) observed a 42% MT incidence in a colony whose mean life span was given as 630 days; their value is shown as a single point at 900 days. Syndor et al. (51) specified both the MT incidence and the age at which the specific observation was made.

The age-incidence data of Shellabarger et al. (18), Vogel and Jordan (20), and Hartwig et al. (21) were more extensive; several points were available from each paper. The laboratory routine used by Shellabarger et al. was such that their age at MT appearance and that used in this study are very close. The other two authors (20, 21) made no mention of tumor size in relation to the age at which an animal was scored as a MT bearer. If the tumors were already large when seen, the placement of these data on the age scale of Chart 9 may err on the high side by as much as 60 days.

Spontaneous MT incidence observed over the past 10 years in other laboratories was within the variation we observed among control groups up to the 600th day. The results of Shellabarger et al. and Vogel and Jordan agreed with this report through the 700th day.

Vogel and Jordan's colony had not died out at the time their report was written, and complete life-span data were not available for their rats. However, rats in the Argonne Laboratory colony are raised under essentially the same conditions as the "COBS" rats from our supplier, and continued agreement with our results is expected.

All the other authors, except Syndor et al., whose colony contained only young rats, reported a high mortality from pulmonary infection. The high rate of early deaths from lung disease rendered the results of Hartwig et al. almost meaningless. The $\chi^2$ test for goodness of fit (47) indicated that our crude result of 61.7% MT was not different from the result reported by Davis et al., 54.8%. Our actuarially corrected result, 71.5%, was significantly higher than any other so far reported.

Comparison of Charts 3 and 9 suggests that the early sacrifices in the $Ca^{45}$ group and the early losses of rats from infections had the same net effect -- a trailing off of the MT incidence at the beginning of the third year. Inasmuch as we endeavored without success to correct for the early losses suffered by the

$Ca^{45}$ group, it would appear that if there is as much as a 30% loss of animals after the 400th day of life an intractable error is introduced into the life-span MT incidence. Smaller losses, such as those sustained by lot I and lot A, evidently can be corrected for without introducing a substantial error.

Our own experience with several normally ageing groups purchased from a single supplier over several years, and the agreement of our results with those from other laboratories using rats bred by other suppliers (at least until pulmonary infections supervene), lead us to conclude that the MT incidence of the female Sprague-Dawley rat is a characteristic which has remained quite stable through many generations. Not only is the MT incidence over the whole life span a reproducible quantity, but MT incidence can also be predicted at any age within relatively narrow limits.

As expected, hormonal manipulations that affect induced or implanted MT in rats also affected development of spontaneous MT in the same direction and to about the same degree. Ovariectomy postponed the onset of the first MT and reduced overall MT incidence almost to the vanishing point. Simultaneous removal of the ovaries and adrenal glands prevented development of MT altogether. Uniparity was without effect, while thyroid deficiency slightly postponed MT development in the second half of the life span.

Furth and his co-workers (5, 37, 45, 52) have implicated the estrogen-stimulated pituitary and mammosomatotropic pituitary tumors in the etiology of carcinogen-induced MT in the rat. Although a full discussion of the relationships between spontaneous MT and age-related changes in the pituitary, ovaries, and adrenals is beyond the scope of this paper, some interesting coincidences are worth noting.

Spontaneous MT began to appear in significant numbers in the latter half of reproductive life. There was a sharp upturn in the rate of MT development at about the time menopause is reported to occur in the rat -- 450 to 540 days

of age (53, 54); preliminary examination of other tissues from the rats in this study indicated that microscopic adenomas and small tumors of the pituitary and microscopic adrenal adenomas began to appear at about this same age (55). There was a second marked increase in the MT incidence rate near the end of the second year; during this period of life -- from 600 to 800 days of age -- the great majority of rats coming to autopsy bore adrenal adenomas or microscopic or gross pituitary adenomas, and the breast was highly developed, ranging from hyperplastic to actively secretory (54).

The dominant role played by pituitary mammotropes in the etiology of induced MT, as postulated by Furth et al., appears to be repeated in the case of spontaneous MT. It is suggested that the postmenopausal ovary provides sufficient estrogen (53) to stimulate the pituitary which in turn provides the hormonal stimulation of the breast, leading to hyperplasia and occult lactation, and in a genetically susceptible strain such as Sprague-Dawley to spontaneous MT.

## FOOTNOTES

1. Work performed under auspices of the U. S. Atomic Energy Commission.
2. Providence Hospital, Portland, Oregon.
3. Bond et al. (23) showed that irradiation of breast tissue was necessary for inducement of MT by x-rays, and that an x-ray dose as small as 25 r increased MT above control levels. The radiation doses to the breast tissue of the $Ca^{45}$-injected and $Sr^{85}$-injected rats were calculated from the integrated plasma curves for these two radioisotopes and were less than 0.1 r from $Ca^{45}$ and less than 0.01 r from $Sr^{85}$. These amounts of radiation were considered insignificant, and the animals in these groups were included as normal controls.
4. Other authors (16, 18) differentiate three classes of benign rat breast tumors -- adenoma, adenofibroma, and fibroadenoma. It was our experience that all three forms could be found in a single MT or even in different areas of the same section of a single MT (42). We chose to classify all benign MT with an epithelial component as fibroadenomata (FA), a practice also used by Millar and Noble (29).
5. A duplicate set of the punched animal data cards is available from the authors on request.

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TABLE 1

SHIPMENT DESIGNATION; BIRTH DATE; NUMBER OF RATS PER GROUP (OR SHIPMENT) THAT SURVIVED ONE YEAR OR MORE; AND SPECIAL TREATMENT, IF ANY.

| LOT NUMBER | BIRTHDATE | SPECIAL DESIGNATIONS OR SUB-GROUPS | NUMBER OF RATS |
|---|---|---|---|
| 1 | 9-15-59 | I - Life span and normal tissue samples | 46 |
| | | $Ca^{45}$ - 10μC $Ca^{45}$ at 110 days; periodic sacrifices | 101 |
| | | TX - Surgical thyroidectomy at 85 days | 45 |
| | | OX - Surgical oophorectomy at 77 days | 45 |
| A | 2-10-60 | $F_1$ generation of 22 rats from lot number 1 | 60 |
| 5 | 4-9-60 | ADX-OX - Surgical adrenalectomy and ovariectomy at 110 days | 4 |
| 6 | 6-18-60 | ADX-OX - Surgical adrenalectomy and ovariectomy at 104 days | 9 |
| 8 | 5-7-60 | ADX-OX - Surgical adrenalectomy and ovariectomy at 95 days | 12 |
| 9 | 8-12-60 | ADX-OX - Surgical adrenalectomy and ovariectomy at 102 days | 26 |
| 11 | 9-4-61 | Life span; 10 each received 10μC $Sr^{85}$ 300, 600 or 700 days | 39 |
| 12 | 7-4-61 | Life span | 44 |
| 14 | 6-16-62 | Life span; 10 each received 10μC $Sr^{85}$ 32 or 400 days | 121 |
| 15 | 5-16-62 | UP Bred at 70 days, delivered and nursed one litter. | 53 |
| 17 | 6-5-63 | Life span; 10 received 10μC $Sr^{85}$ at 159 days | 84 |

TABLE 2

PERCENT OF RATS IN CONTROL AND EXPERIMENTAL GROUPS THAT DEVELOPED AT LEAST ONE MAMMARY TUMOR BASED ON (a) THE TOTAL NUMBER OF RATS PER GROUP AT START -- CRUDE INCIDENCE; OR (b) POPULATION ACTUARIALLY CORRECTED FOR EXTRANEOUS DEATHS -- CORRECTED INCIDENCE (44).

| | CONTROL GROUPS | | | | | | | | EXPERIMENTAL GROUPS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | $Ca^{45}$ | A | 11 | 12 | 14-1 | 14-2 | 17 | UP | TX | OX | ADX-OX |
| PERCENT MAMMARY TUMORS CRUDE | | | | | | | | | | | | |
| LIFE SPAN | 65.2 | 47.5 | 58.3 | 61.5 | 77.3 | 60.0 | 62.3 | - | 52.8 | 71.1 | 3.9 | 0 |
| PERCENT MAMMARY TUMORS CORRECTED | | | | | | | | | | | | |
| LIFE SPAN | 78.9 | 60.8 | 67.3 | 63.2 | 77.3 | 73.5 | 66.7 | - | 70.0 | 71.1 | 3.9 | 0 |
| 900 DAYS | 76.3 | 58.2 | 59.6 | 60.5 | 75.0 | 73.5 | 64.9 | - | 60.0 | 60.0 | 3.2 | - |
| 660 DAYS | 26.3 | 24.5 | 22.6 | 33.3 | 56.8 | 28.1 | 32.2 | 37.6 | 22.4 | 19.9 | 2.4 | - |

TABLE 3

AGE DISTRIBUTION BY QUARTILE OF THE APPEARANCE OF MAMMARY TUMORS (FIRST MAMMARY TUMOR PER RAT) MAXIMUM LIFE SPAN AND MEDIAN AGE TO MAMMARY TUMOR OR DEATH IN CONTROL AND EXPERIMENTAL GROUPS

| | CONTROL GROUPS | | | | | | | | EXPERIMENTAL GROUPS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | $Ca^{45}$ | A | 11 | 12 | 14-1 | 14-2 | 17 | UP | TX | OX | ADX-OX |
| FIRST MAMMARY TUMOR | 317 | 305 | 441 | 240 | 298 | 212 | 341 | 313 | 106 | 309 | 638 | - |
| 25TH PERCENTILE | 584 | 577 | 618 | 539 | 454 | 524 | 568 | - | 579 | 643 | - | - |
| 50TH PERCENTILE (MEDIAN MAMMARY TUMOR) | 709 | 690 | 715 | 637 | 593 | 677 | 675 | - | 713 | 784 | 930 | - |
| 75TH PERCENTILE | 736 | 821 | 841 | 819 | 660 | 727 | 707 | - | 822 | 819 | - | - |
| 100TH PERCENTILE (LAST MAMMARY TUMOR) | 957 | 1002 | 1010 | 912 | 905 | 885 | 943 | - | 945 | 1143 | 969 | - |
| MAXIMUM LIFE SPAN | 975 | 1008 | 1040 | 961 | 987 | 919 | 940 | - | 971 | 1143 | 1295 | 1110 |
| MEDIAN LIFE SPAN (MAMMARY TUMOR OR DEATH) | 682 | 691 | 749 | 670 | 625 | 656 | 657 | - | 689 | 751 | 1011 | 881 |

TABLE 4

TUMORS OF SKIN AND SUBCUTANEOUS TISSUES, OTHER THAN MAMMARY TISSUE

| | CONTROLS* | TX | OX | ADX-OX |
|---|---|---|---|---|
| NUMBER OF RATS | 548 | 45 | 44 | 51 |
| FIBROSARCOMA | 7 | 2 | | 1 |
| SARCOMA | 1 | | | |
| OSTEOGENIC SARCOMA | 4 | 1 | 1 | |
| RETICULUM CELL SARCOMA | 1 | | | |
| NEUROFIBROSARCOMA | 1 | | | |
| SYNOVIAL SARCOMA | 1 | | | |
| ANGIOSARCOMA | 1 | | | |
| FIBROMA | 3 | 1 | | 2 |
| LIPOMA | 4 | | 2 | |
| NEUROFIBROMA | 1 | | | |
| MYXOFIBROMA | | | 1 | |
| BASAL CELL CARCINOMA | 3 | | 1 | |
| SQUAMOUS CELL CARCINOMA | 1 | | | |
| SEBACEOUS CELL ADENOMA | 2 | | | |
| HEMATOMA | | | | 1 |
| GRANULOMA | | | 1 | |

*All untreated rats including uniparous group, and lot A (born at Crocker).

TABLE 5

MAMMARY CARCINOMA AND CARCINOMA IN SITU ENCOUNTERED AMONG SPONTANEOUS MAMMARY TUMORS OF THE FEMALE SPRAGUE-DAWLEY RAT

| GROUP | MAMMARY TUMOR BEARERS | CA | CA IN SITU | PERCENT CA BEARERS | PERCENT CA PLUS CA IN SITU |
|---|---|---|---|---|---|
| LOT A | 35 | 0 | 1 | 0 | 2.8 |
| LOT 11 | 24 | 7 | 1 | 29.2 | 33.3 |
| LOT 12 | 34 | 1 | 5 | 2.9 | 17.6 |
| LOT 14 | 74 | 19 | 7 | 25.7 | 35.1 |
| LOT 17[a] | 32 | 12 | 3 | 37.5 | 46.9 |
| LOT 1 (I + $Ca^{45}$) | 78 | 6 | 4 | 7.7 | 12.8 |
| UP (LOT 15) | 28 | 10 | 2 | 35.7 | 42.9 |
| TX (LOT 1) | 32 | 4 | 0 | 12.5 | 12.5 |
| OX(LOT 1) | 3 | 2 | 0 | 66.7 | 66.7 |
| ADX-OX | 0 | - | - | - | - |
| ALL CONTROLS FROM CHARLES RIVER[b] | 242 | 45 | 20 | 18.6 | 26.8 |
| Standard Deviation Weighted for Group Size | | | | ±12.1 | ±12.4 |

[a] 23 Rats Still Alive without Mammary Tumor at 700 Days of Age

[b] Lots I-$Ca^{45}$, 11, 12, 14, 17

# APPENDIX

The life tables of mammary tumor development and of mortality without tumor are shown for the various control and experimental groups in Appendix Tables 1 through 14. An explanation of the column headings in the Tables follows:

Col. 1, Age at end of interval: The age of the colony at the end of each 30-day actuarial interval.

Col. 2, MT: The number of rats developing a first mammary tumor in the interval.

Col. 3, Deaths: Deaths of rats without tumor, including deaths due to other neoplasms or degenerative diseases, and deaths for which cause was not determinable.

Col. 4, Extraneous deaths: Deaths of rats (without tumor) known to be totally unrelated to mammary tumor development, i.e., deliberate sacrifice of rats for other experiments, accidental deaths, or deaths from proven pulmonary infection.

Col. 5, Corrected population: The corrected population, which takes into account loss of rats from extraneous causes (Col. 4). This actuarial correction, due to Berkson and Gage assumes that rats dying in the interval lived, on the average, for half the interval: Corr. pop. = Pop. at start of interval - 0.5 (Extran. deaths).

Col. 6, Cumulative MT: Total number of mammary tumor bearers to the end of this interval.

Col. 7, % Cumulative MT: Percentage of mammary tumor bearers in the corrected population: % Cum MT = (Cum. MT/Corr. pop.)$\times$100.

Col. 8, Population at start: Rats surviving without tumor to start of interval: Pop. at $\text{start}_2$ = Pop. at $\text{start}_1$ - ($\text{MT}_1$ + $\text{Deaths}_1$ + Extran. $\text{deaths}_1$), where the subscripts refer to succeeding intervals $i_1$, $i_2$, $i_3$, $i_n$.

Col. 9, Rats at risk for month: Number of rats available to develop a first mammary tumor during interval: Rats at risk = Pop. at start - 0.5(all deaths in interval).

Col. 10, % MT/rat-month: Percentage of rats at risk developing a first mammary tumor during interval: % MT/rat-month = (Mt/Pop. at risk for month)×100. This is also a measure of the probability of development of a first mammary tumor at a given age; or, in actuarial terms, a measure of the rate at which the members of a life table are dying out because of development of mammary tumors.

## FIGURE LEGENDS

1. Growth curve of the "average" mammary fibroadenoma of the Sprague-Dawley rat.
2. Cumulative incidence of spontaneous mammary tumors (MT) in five groups of virgin female Sprague-Dawley rats obtained from the Charles River Laboratories between September 1959 and June 1963.
3. Influence of the sacrifice of healthy nontumorous rats on the cumulative life span incidence of MT. All rats were received in the same shipment (lot 1). The $Ca^{45}$ group suffered periodic losses to meet a predetermined sacrifice schedule; their controls (lot I) were undisturbed.
4. Influence of thyroidectomy at 85 days of age on the incidence of MT over the life span.
5. Survival without a MT in five groups of virgin controls. Arrows indicate the range in age at which sharp changes in slope occurred.
6. Survival without a MT of the combined group of Charles River controls compared to MT morbidity of uniparous, thyroidectomized, and outbred (lot A) rats. Arrows indicate the control range of changes in slope of the survival curves. These inflections (points of change) are labeled 1 and 2 on the control curve.
7. Force of mortality from MT, i.e., the change in rate of MT development with age, in the three large control groups (Lots 1, 14, and 17). The heavy black line represents the combined data from all control groups. Probability of development of a MT is obtained by multiplying $\mu(x)$ at any age by $10^{-2}$.
8. The frequency distribution at different ages of mammary carcinoma and fibroadenoma. Data were taken from all endocrinologically intact groups and includes Lots I, 11, 12, 14, 17, $Ca^{45}$, A, and UP.

9. Comparison of the cumulative incidence of spontaneous MT observed in this Laboratory with published results for the Sprague-Dawley strain. Circled letters refer to the source of single values: Ⓓ, David et al. (34), Ⓢ, Syndor et al. (51), and Ⓣ, Thompson et al. (38).

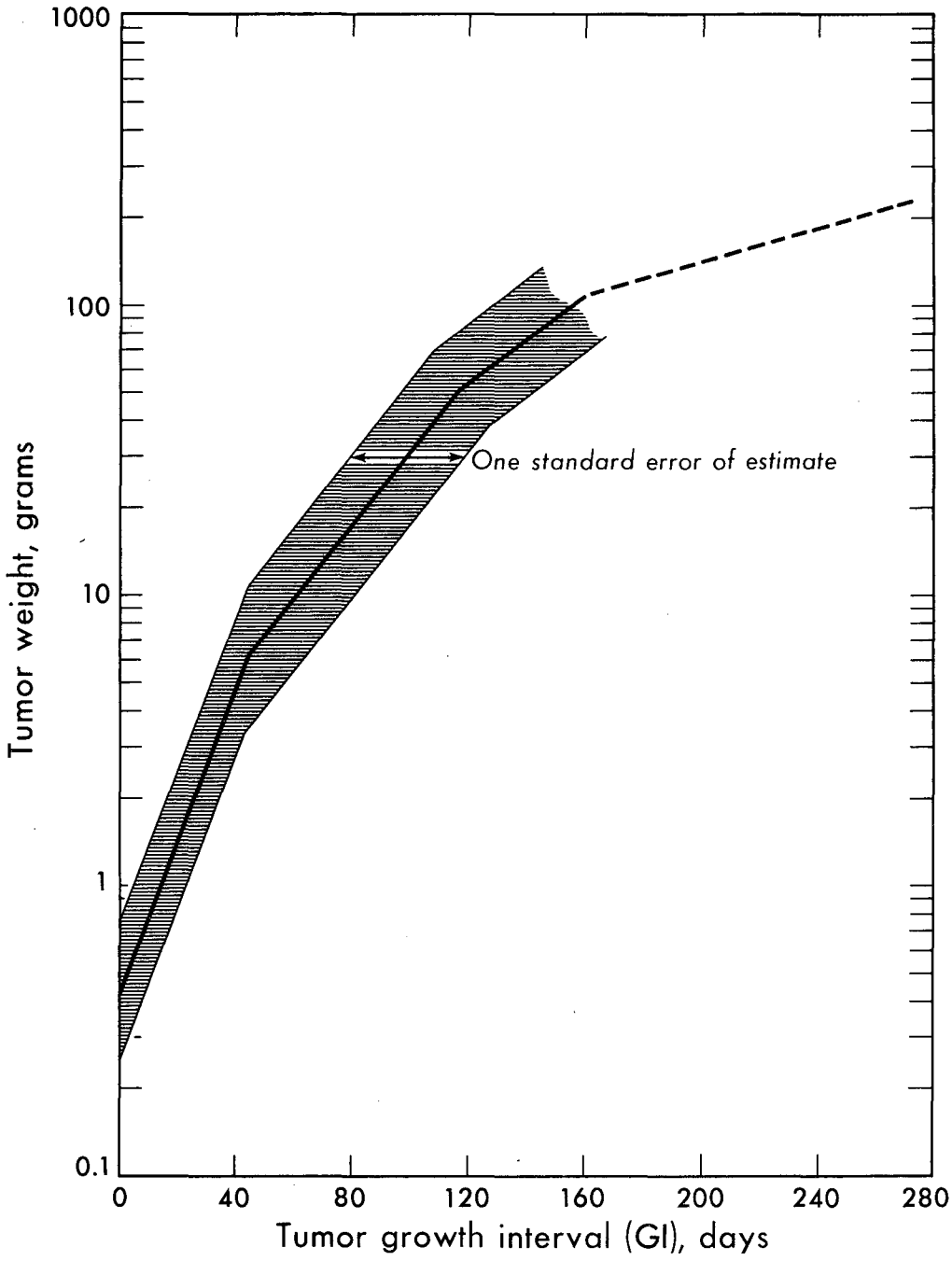

1000
100
10
1
0.1
Tumor weight, grams
One standard error of estimate
0
40
80
120
160
200
240
280
Tumor growth interval (GI), days
MUB-6673

Chart 1

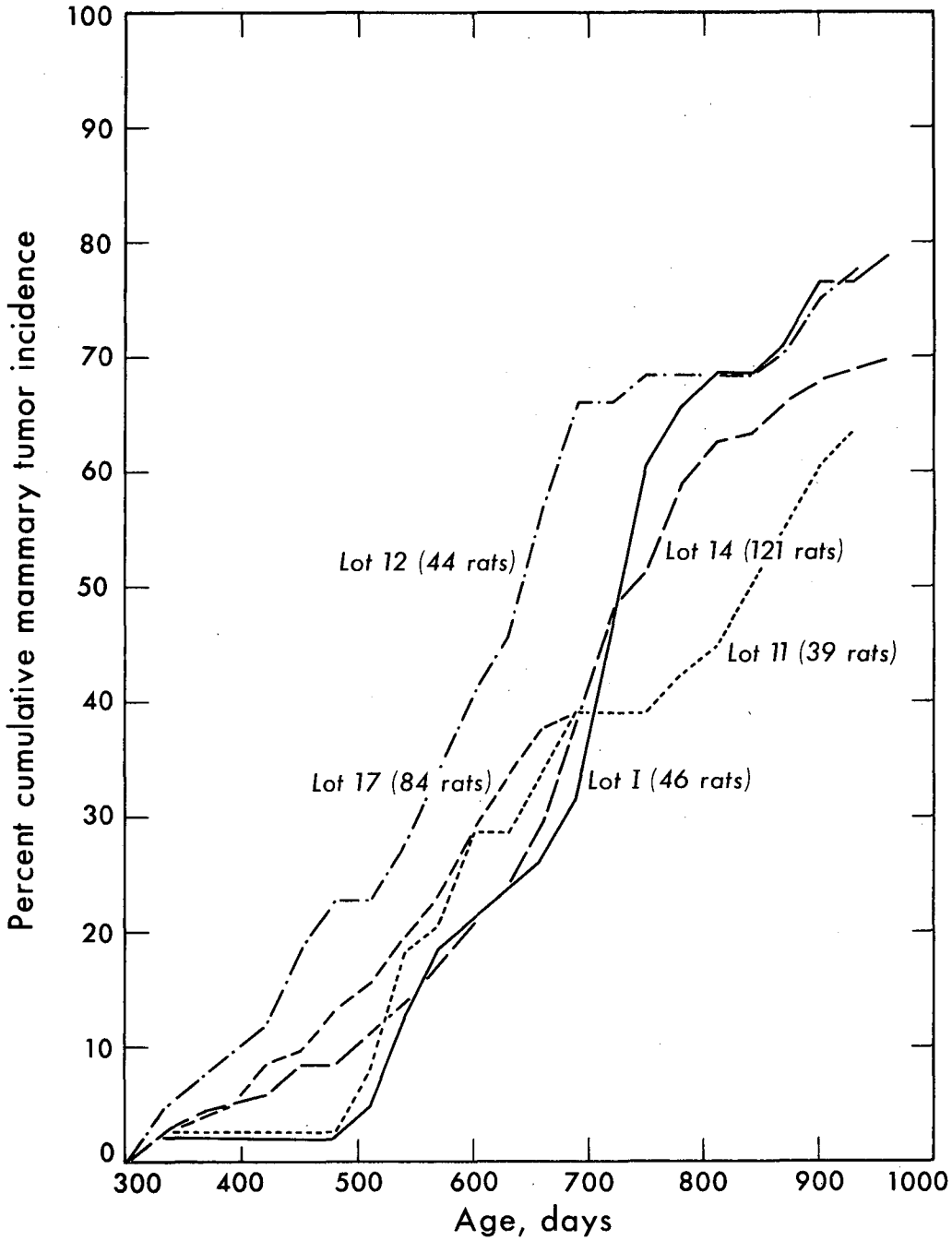

Percent cumulative mammary tumor incidence
100
90
80
70
60
50
40
30
20
10
0
300
400
500
600
700
800
900
1000
Age, days
Lot 12 (44 rats)
Lot 14 (121 rats)
Lot 11 (39 rats)
Lot 17 (84 rats)
Lot I (46 rats)
MUB-6674

Chart 2

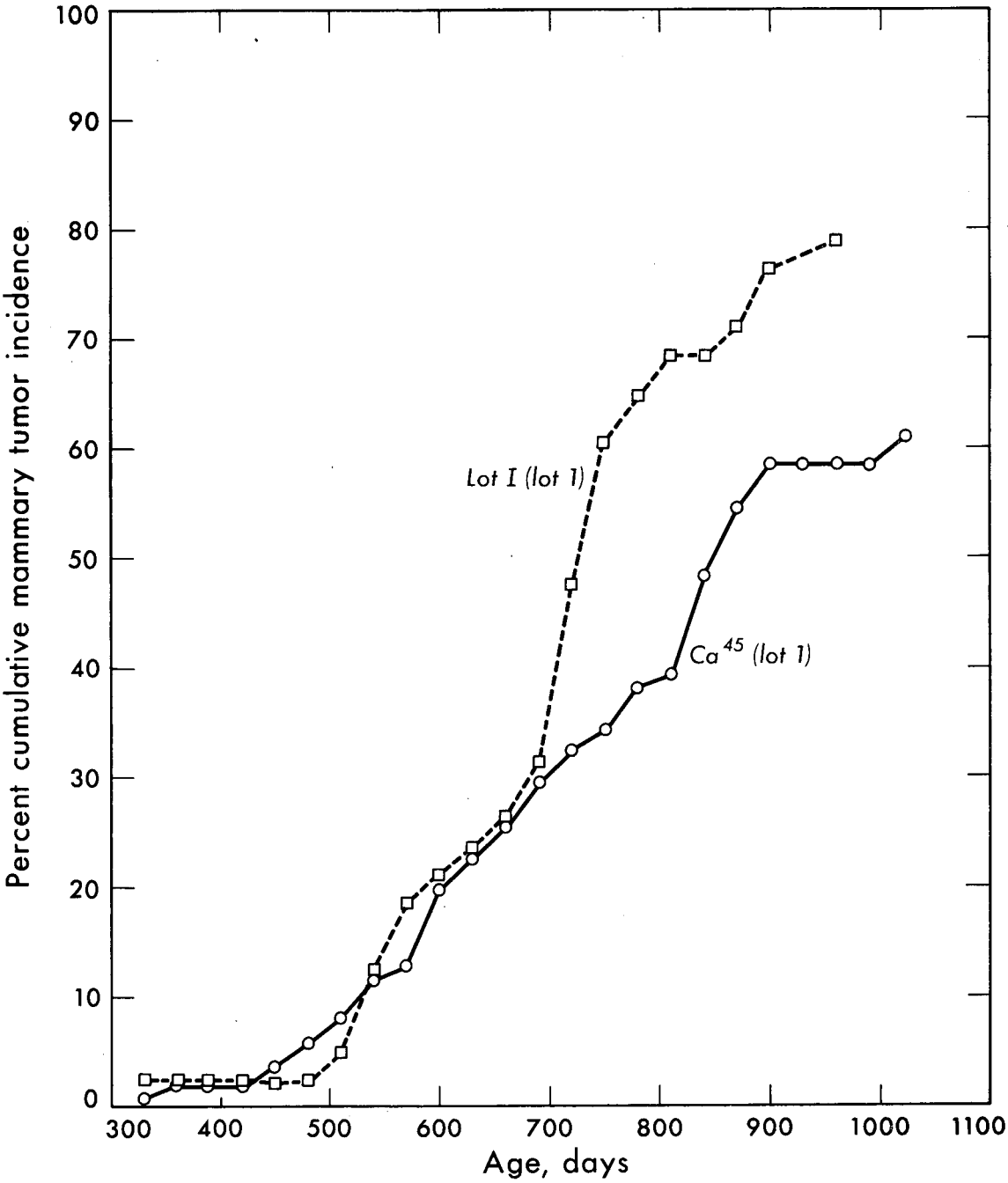

Percent cumulative mammary tumor incidence
100
90
80
70
60
50
40
30
20
10
0
300
400
500
600
700
800
900
1000
1100
Age, days
Lot I (lot 1)
Ca 45 (lot 1)
MUB-6675

Chart 3

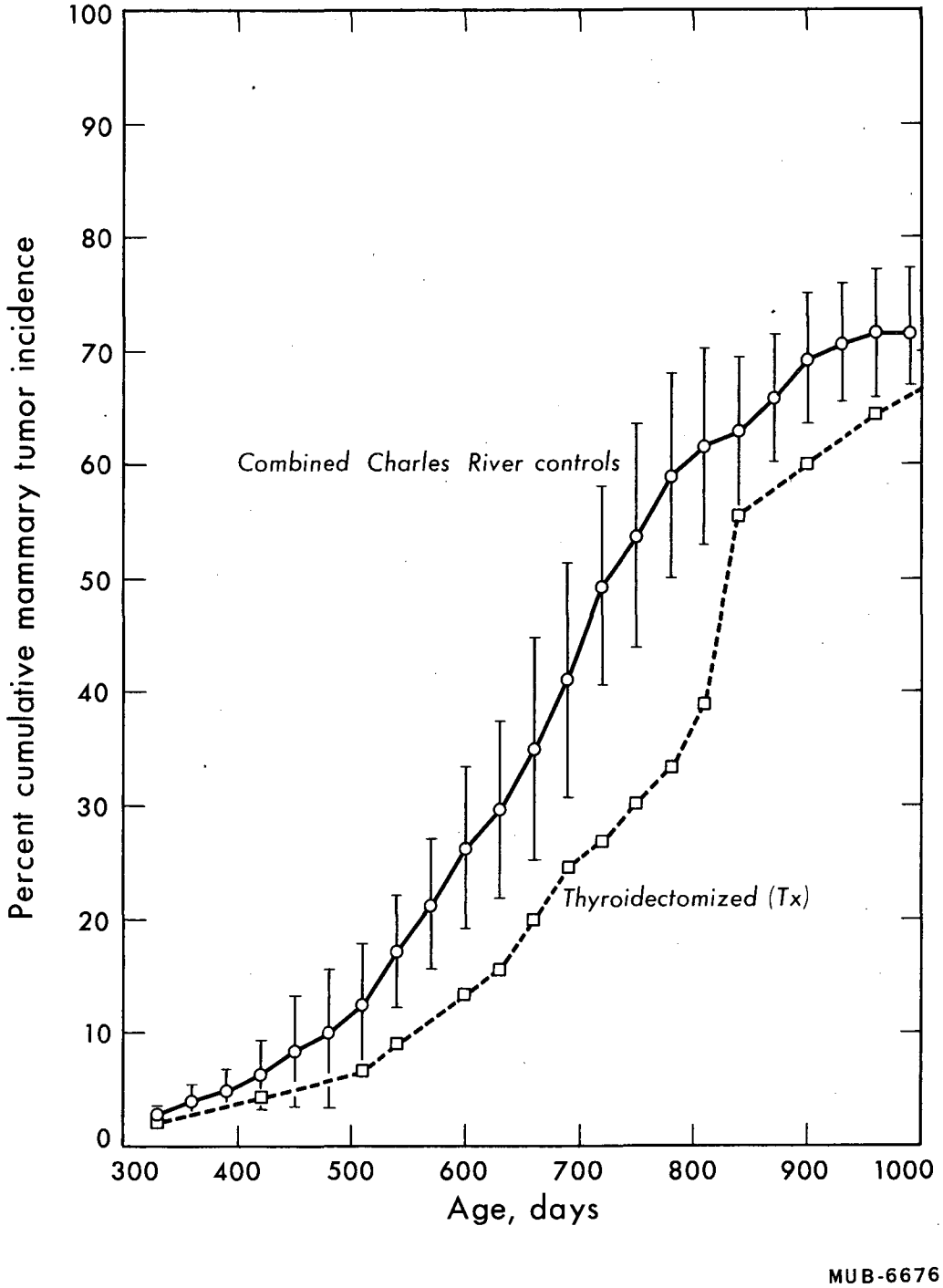
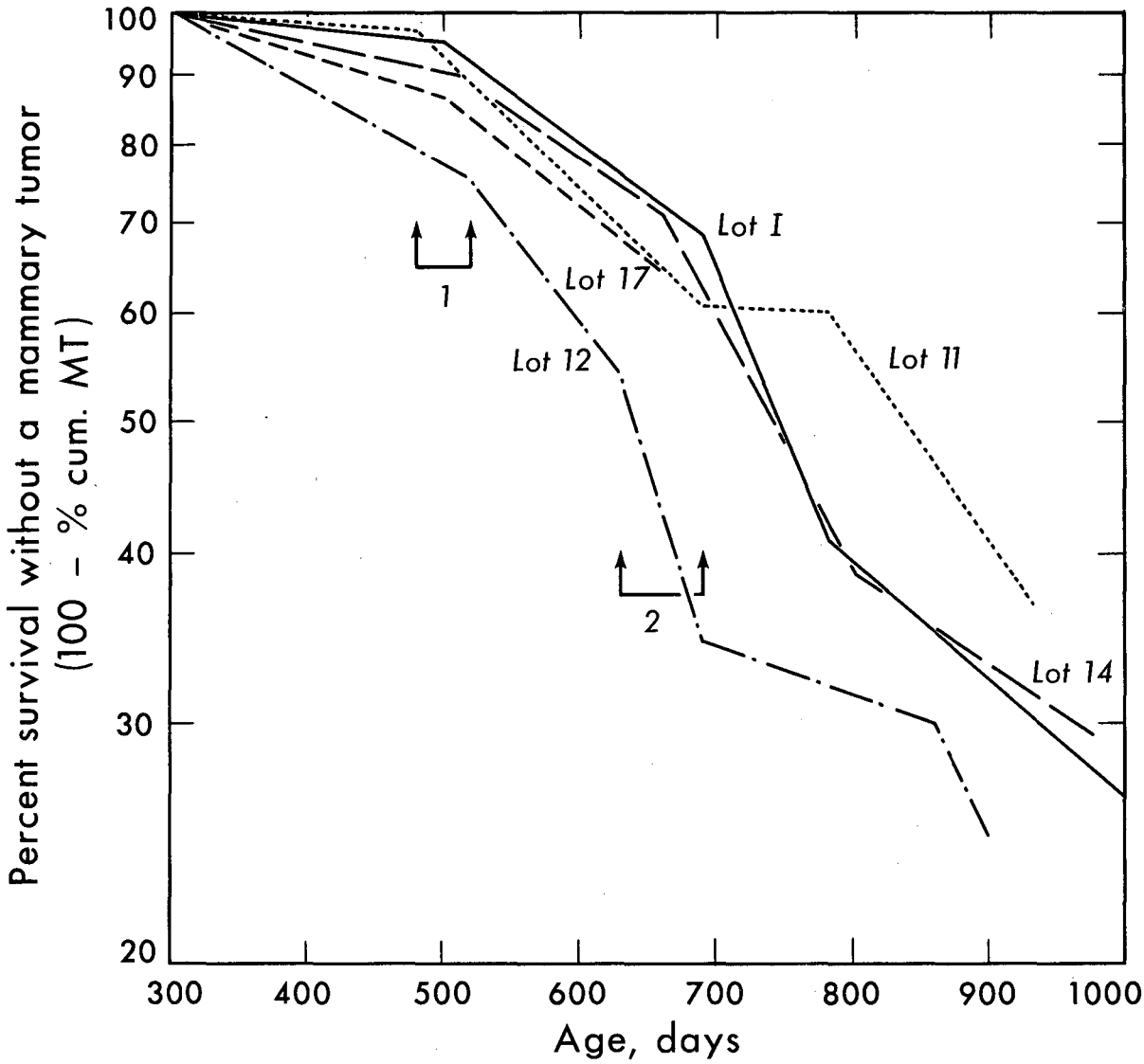
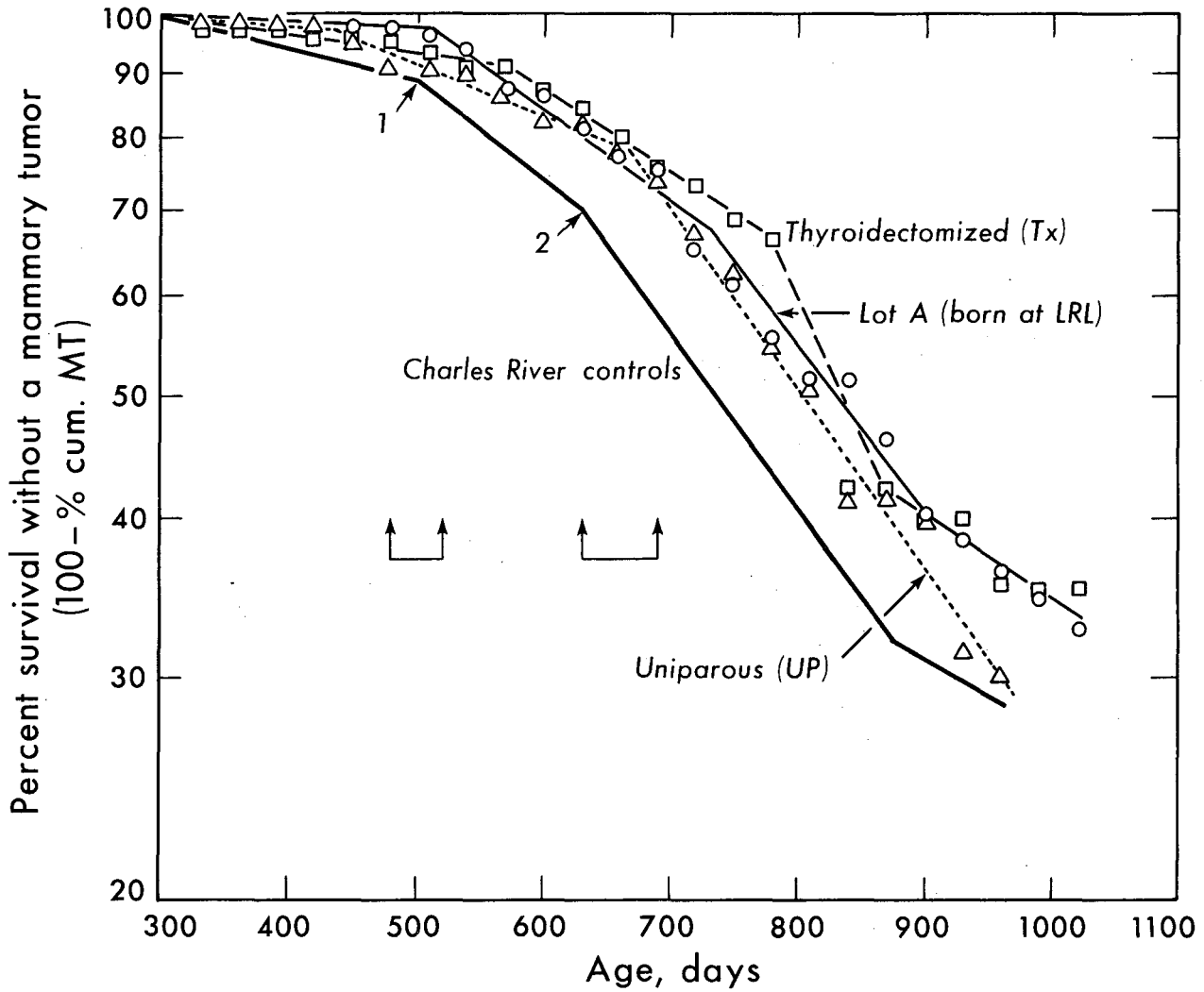

Percent cumulative mammary tumor incidence
100
90
80
70
60
50
40
30
20
10
0
300
400
500
600
700
800
900
1000
Age, days
Combined Charles River controls
Thyroidectomized (Tx)
MUB-6676

Chart 4




MUB-6677

Chart 5




MUB-6678

Chart 6

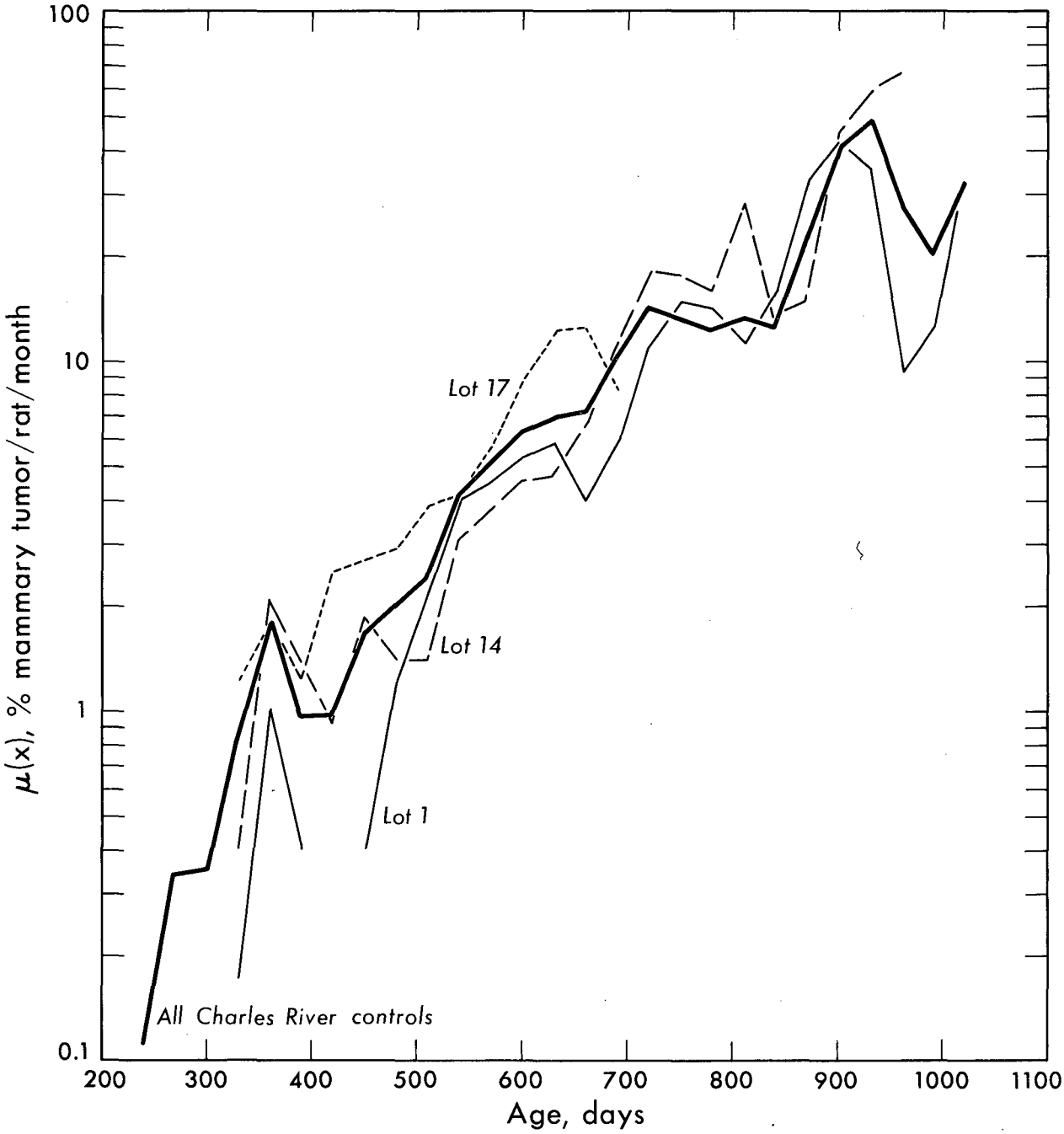

100
10
1
0.1
μ(x), % mammary tumor/rat/month
200
300
400
500
600
700
800
900
1000
1100
Age, days
Lot 17
Lot 14
Lot 1
All Charles River controls
MUB-6679

Chart 7

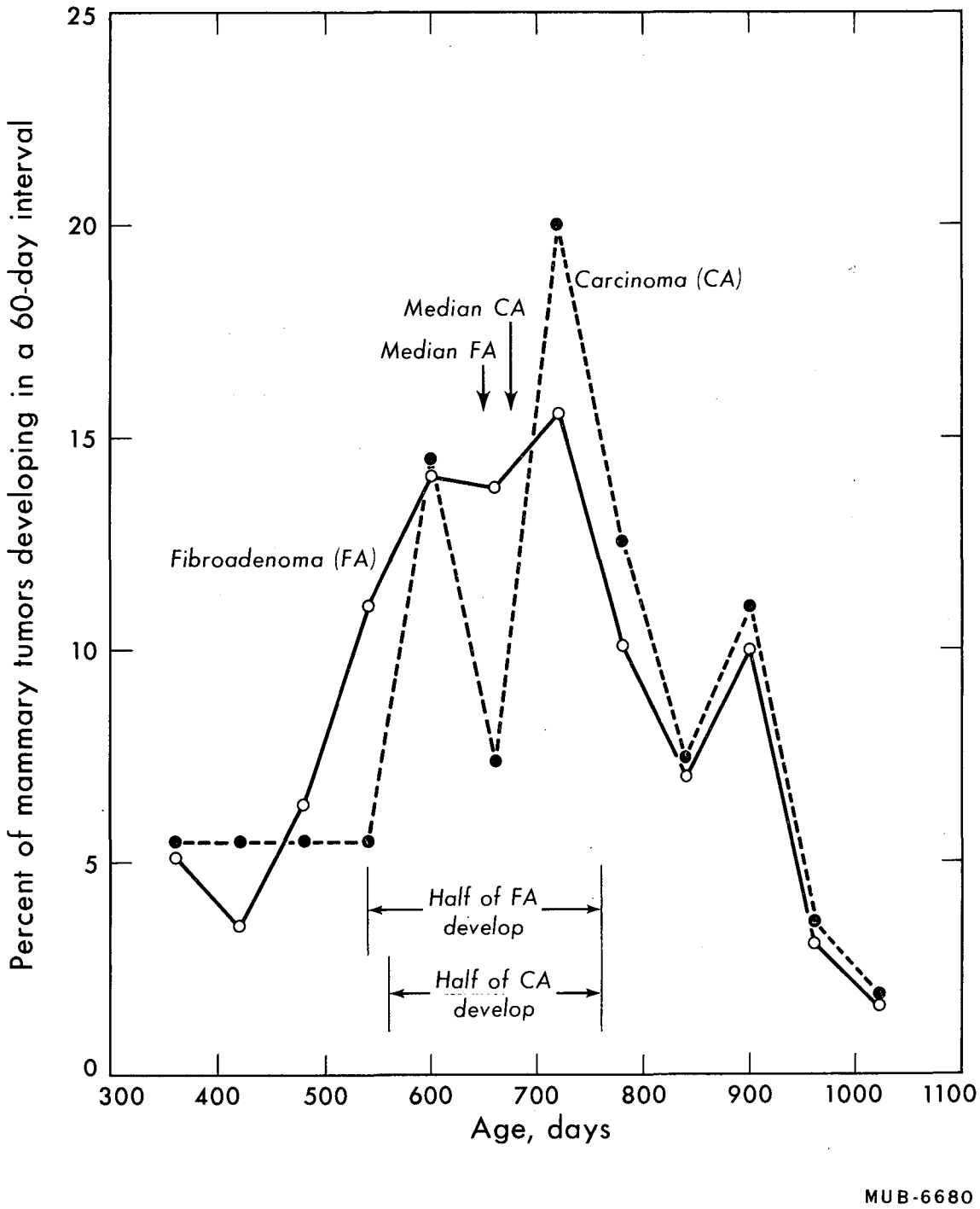

Percent of mammary tumors developing in a 60-day interval
25
20
15
10
5
0
300
400
500
600
700
800
900
1000
1100
Age, days
Carcinoma (CA)
Median CA
Median FA
Fibroadenoma (FA)
Half of FA develop
Half of CA develop
MUB-6680

Chart 8

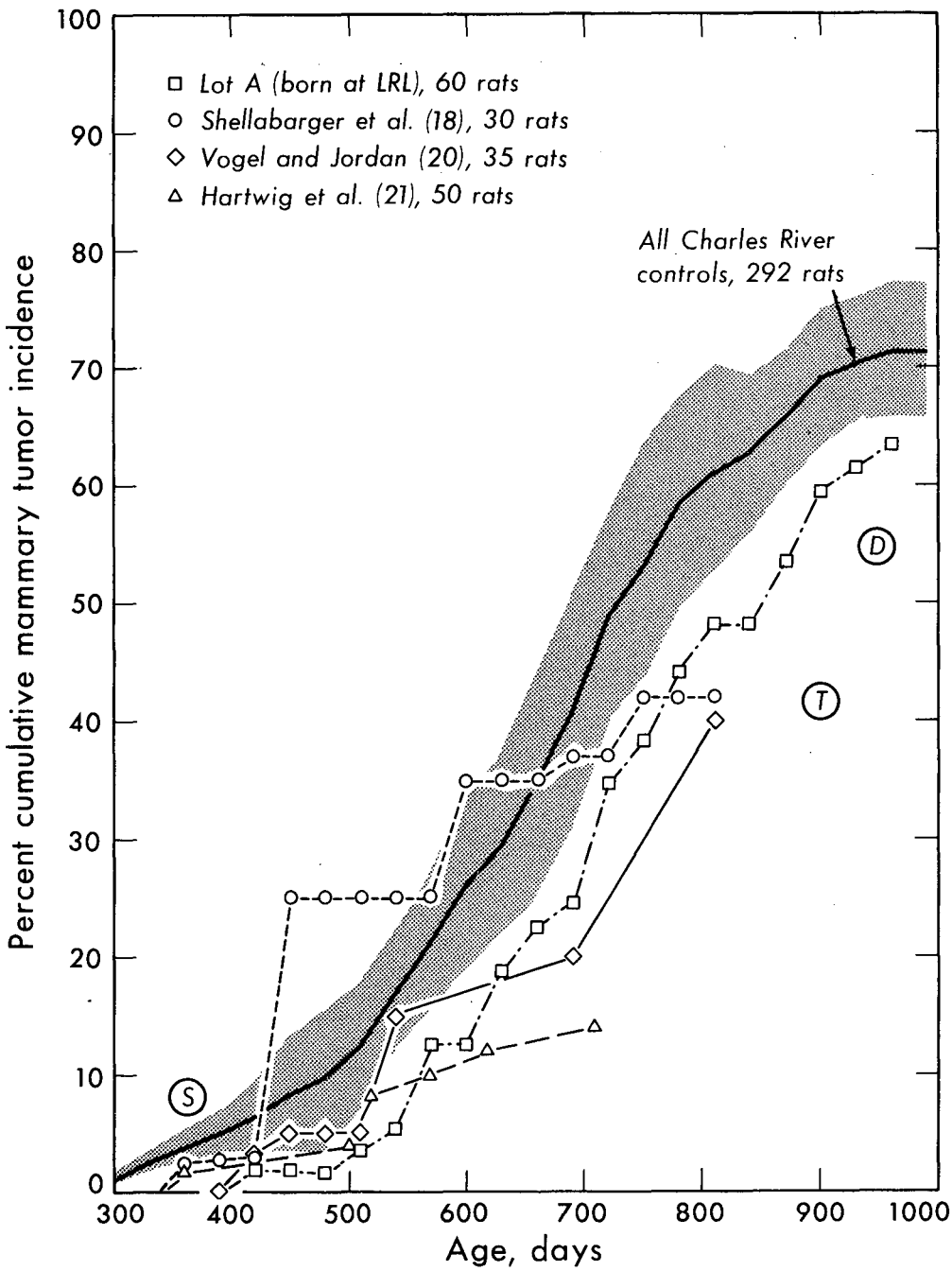

Lot A (born at LRL), 60 rats
Shellabarger et al. (18), 30 rats
Vogel and Jordan (20), 35 rats
Hartwig et al. (21), 50 rats
All Charles River controls, 292 rats
S
D
T
Percent cumulative mammary tumor incidence
Age, days
0
10
20
30
40
50
60
70
80
90
100
300
400
500
600
700
800
900
1000
MUB-6681

Chart 9

Appendix

Table 1. Life table, Lot 1, $Ca^{45}$-injected rats.

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT rat-month |
| 300-330 | 1 | | | 101 | 1 | 1.0 | 101 | 101 | 1.0 |
| 360 | 1 | | | 101 | 2 | 2.0 | 100 | 100 | 1.0 |
| 390 | | | 4 | 99 | 2 | 2.0 | 99 | 97 | |
| 420 | | | 6 | 94 | 2 | 2.0 | 95 | 92 | |
| 450 | 1 | | 4 | 89 | 3 | 3.4 | 89 | 87 | 1.1 |
| 480 | 2 | 1 | | 87 | 5 | 5.7 | 84 | 83.5 | 2.4 |
| 510 | 2 | 3 | | 87 | 7 | 8.0 | 81 | 79.5 | 2.5 |
| 540 | 3 | 1 | | 87 | 10 | 11.5 | 76 | 75.5 | 4.0 |
| 570 | 1 | 3 | 1 | 86.5 | 11 | 12.7 | 72 | 70 | 1.4 |
| 600 | 6 | 1 | | 86 | 17 | 19.8 | 67 | 66.5 | 9.0 |
| 630 | 2 | 1 | 2 | 85 | 19 | 22.4 | 60 | 58.5 | 3.4 |
| 660 | 2 | 4 | 3 | 82.5 | 21 | 25.4 | 55 | 51.5 | 3.9 |
| 690 | 3 | 2 | | 81 | 24 | 29.6 | 46 | 45 | 6.7 |
| 720 | 2 | 5 | 2 | 80 | 26 | 32.5 | 41 | 37.5 | 5.3 |
| 750 | 1 | | | 79 | 27 | 34.2 | 32 | 32 | 3.1 |
| 780 | 3 | 3 | | | 30 | 38.0 | 31 | 29.5 | 10.2 |
| 810 | 1 | 1 | | | 31 | 39.2 | 25 | 24.5 | 4.1 |
| 840 | 7 | 1 | | | 38 | 48.1 | 23 | 22.5 | 31.1 |
| 870 | 5 | 1 | | | 43 | 54.4 | 15 | 14.5 | 34.5 |
| 900 | 3 | | | | 46 | 58.2 | 9 | 9 | 33.3 |
| 930 | | 1 | | | 46 | 58.2 | 6 | 5.5 | |
| 960 | | 1 | | | 46 | 58.2 | 5 | 4.5 | |
| 990 | | | | | 46 | 58.2 | 4 | 4 | |
| 1020 | 2 | 2 | | | 48 | 60.8 | 4 | 3 | 66.7 |

Appendix

Table 2. Life table, Lot 1.

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT rat-month |
| 300-330 | 1 | | | 46 | 1 | 2.2 | 46 | 46 | 2.2 |
| 360 | | | | | 1 | 2.2 | 45 | 45 | |
| 390 | | | | | 1 | 2.2 | 45 | 45 | |
| 420 | | | | | 1 | 2.2 | 45 | 45 | |
| 450 | | 1 | | | 1 | 2.2 | 45 | 44.5 | |
| 480 | | | 5 | 43.5 | 1 | 2.2 | 44 | 41.5 | |
| 510 | 1 | | | 41 | 2 | 4.9 | 39 | 39 | 2.6 |
| 540 | 3 | 1 | 3 | 39.5 | 5 | 12.6 | 38 | 36 | 8.3 |
| 570 | 2 | | | 38 | 7 | 18.4 | 31 | 31 | 6.4 |
| 600 | 1 | 1 | | | 8 | 21.0 | 29 | 28.5 | 3.5 |
| 630 | 1 | 1 | | | 9 | 23.7 | 27 | 27.5 | 3.6 |
| 660 | 1 | | | | 10 | 26.3 | 25 | 25 | 4.0 |
| 690 | 2 | | | | 12 | 31.6 | 24 | 24 | 8.3 |
| 720 | 6 | | | | 18 | 47.4 | 22 | 22 | 27.3 |
| 750 | 5 | 1 | | | 23 | 60.5 | 16 | 15.5 | 32.2 |
| 780 | 2 | 1 | | | 25 | 65.8 | 10 | 9.5 | 21.0 |
| 810 | 1 | | | | 26 | 68.4 | 7 | 7 | 14.3 |
| 840 | | | | | 26 | 68.4 | 6 | 6 | |
| 870 | 1 | | | | 27 | 71.0 | 6 | 6 | 16.7 |
| 900 | 2 | 2 | | | 29 | 76.3 | 5 | 4 | 50.0 |
| 930 | | | | | 29 | 76.3 | 1 | 1 | |
| 960 | 1 | | | | 30 | 78.9 | 1 | 1 | 100.0 |

Appendix

Table 3. Life table, Lot 1 ($Ca^{45}$-injected and Lot I combined).

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT / rat-month |
| 300-330 | 2 | | | 147 | 2 | 1.4 | 147 | 147 | 1.4 |
| 360 | 1 | | | 147 | 3 | 2.0 | 145 | 145 | 0.7 |
| 390 | | | 4 | 146 | 3 | 2.0 | 144 | 142 | |
| 420 | | | 6 | 144 | 3 | 2.1 | 140 | 137 | |
| 450 | 1 | 1 | 4 | 135 | 4 | 3.0 | 134 | 131.5 | 0.8 |
| 480 | 2 | 1 | 5 | 130.5 | 6 | 4.6 | 128 | 125 | 1.6 |
| 510 | 3 | 3 | | 128 | 9 | 7.0 | 120 | 118.5 | 2.5 |
| 580 | 6 | 2 | 3 | 126.5 | 15 | 11.8 | 114 | 111.5 | 5.4 |
| 570 | 3 | 3 | 1 | 124.5 | 18 | 14.5 | 103 | 101 | 3.0 |
| 600 | 7 | 2 | | 124 | 25 | 20.2 | 96 | 95 | 7.4 |
| 630 | 3 | 2 | 2 | 123 | 28 | 22.8 | 87 | 86 | 3.5 |
| 660 | 3 | 4 | 3 | 120.5 | 31 | 25.7 | 80 | 76.5 | 3.9 |
| 690 | 5 | 2 | | 119 | 36 | 30.2 | 70 | 69 | 7.2 |
| 720 | 8 | 5 | 2 | 118 | 44 | 37.3 | 63 | 59.5 | 13.4 |
| 750 | 6 | 1 | | 117 | 50 | 42.7 | 48 | 47.5 | 12.6 |
| 780 | 5 | 4 | | | 55 | 47.0 | 41 | 39 | 12.8 |
| 810 | 2 | 1 | | | 57 | 48.7 | 32 | 31.5 | 6.3 |
| 840 | 7 | 1 | | | 64 | 54.7 | 29 | 28.5 | 24.6 |
| 870 | 6 | 1 | | | 70 | 59.8 | 21 | 20.5 | 29.3 |
| 900 | 5 | 2 | | | 75 | 64.1 | 14 | 13 | 38.5 |
| 930 | | 1 | | | 75 | 64.1 | 7 | 6.5 | |
| 960 | 1 | 1 | | | 76 | 65.0 | 6 | 5.5 | 18.1 |
| 990 | | | | | 76 | 65.0 | 4 | 4 | 0 |
| 1020 | 2 | 2 | | | 78 | 66.7 | 4 | 3 | 66.6 |

Appendix

Table 4. Life table, Lot 11.

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT / rat-month |
| < 300 | 1 | | | | 1 | 2.6 | 39 | 39 | |
| 300-330 | | | | 39 | 1 | 2.6 | 38 | 38 | |
| 360 | | | | | 1 | 2.6 | 38 | 38 | |
| 390 | | | | | 1 | 2.6 | 38 | 38 | |
| 420 | | | | | 1 | 2.6 | 38 | 38 | |
| 450 | | 1 | | | 1 | 2.6 | 38 | 37.5 | |
| 480 | | 1 | | | 1 | 2.6 | 37 | 36.5 | |
| 510 | 2 | | | | 3 | 7.7 | 36 | 36 | 5.6 |
| 540 | 4 | 1 | | | 7 | 17.9 | 34 | 33.5 | 11.9 |
| 570 | 1 | 2 | | | 8 | 20.5 | 29 | 28 | 3.6 |
| 600 | 3 | | | | 11 | 28.2 | 26 | 26 | 11.5 |
| 630 | | 1 | | | 11 | 28.2 | 23 | 22.5 | |
| 660 | 2 | 1 | | | 13 | 33.3 | 22 | 21.5 | 9.3 |
| 690 | 2 | | 1 | 38.5 | 15 | 39.0 | 19 | 18.5 | 10.8 |
| 720 | | 1 | | 38 | 15 | 39.0 | 16 | 15.5 | |
| 750 | | 1 | | | 15 | 39.0 | 15 | 14.5 | |
| 780 | 1 | | | | 16 | 42.1 | 14 | 14 | 7.1 |
| 810 | 1 | | | | 17 | 44.7 | 13 | 13 | 7.7 |
| 840 | 2 | 2 | | | 19 | 50.0 | 12 | 11 | 18.2 |
| 870 | 2 | 2 | | | 21 | 55.3 | 8 | 7 | 28.5 |
| 900 | 2 | | | | 23 | 60.5 | 4 | 4 | 50.0 |
| 930 | 1 | | | | 24 | 63.2 | 2 | 2 | 50.0 |
| 960 | | | | | 24 | 63.2 | 1 | 1 | |
| 990 | | 1 | | | 24 | 63.2 | 1 | 1 | |

Appendix

Table 5. Life table, Lot 12.

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT rat-month |
| < 300 | 1 | | | | 1 | 2.2 | 44 | 44 | 2.2 |
| 300-330 | 1 | | | 44 | 2 | 4.5 | 43 | 43 | 2.3 |
| 360 | 1 | | | | 3 | 6.8 | 42 | 42 | 2.4 |
| 390 | 1 | | | | 4 | 9.1 | 41 | 41 | 2.4 |
| 420 | 1 | | | | 5 | 11.4 | 40 | 40 | 2.5 |
| 450 | 3 | | | | 8 | 18.2 | 39 | 39 | 7.7 |
| 480 | 2 | | | | 10 | 22.7 | 36 | 36 | 5.6 |
| 510 | | | | | 10 | 22.7 | 34 | 34 | |
| 540 | 2 | | | | 12 | 27.3 | 34 | 34 | 5.9 |
| 570 | 3 | | | | 15 | 34.1 | 32 | 32 | 9.4 |
| 600 | 3 | 2 | | | 18 | 40.9 | 29 | 28 | 10.7 |
| 630 | 2 | 1 | | | 20 | 45.4 | 24 | 23.5 | 8.5 |
| 660 | 5 | | | | 25 | 56.8 | 21 | 21 | 23.8 |
| 690 | 4 | 2 | | | 29 | 65.9 | 16 | 15 | 26.7 |
| 720 | | | | | 29 | 65.9 | 10 | 10 | |
| 750 | 1 | | | | 30 | 68.2 | 10 | 10 | 10.0 |
| 780 | | | | | 30 | 68.2 | 9 | 9 | |
| 810 | | 1 | | | 30 | 68.2 | 9 | 8.5 | |
| 840 | | | | | 30 | 68.2 | 8 | 8 | |
| 870 | 1 | | | | 31 | 70.5 | 8 | 7.5 | 1.3 |
| 900 | 2 | 2 | | | 33 | 75.0 | 6 | 5 | 40.0 |
| 930 | 1 | | | | 34 | 77.3 | 2 | 2 | 50.0 |
| 960 | | | | | 34 | 77.3 | 1 | 1 | |
| 990 | | 1 | | | 34 | 77.3 | 1 | 1 | |

Appendix

Table 6. Life table, Lot 14 (part 1).

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT / rat-month |
| 300-330 | 3 | | | 60 | 3 | 5.0 | 60 | 60 | 5.0 |
| 360 | 1 | | | | 4 | 6.6 | 57 | 57 | 1.8 |
| 390 | | | | | 4 | 6.6 | 56 | 56 | |
| 420 | 1 | | | | 5 | 8.3 | 56 | 56 | 1.8 |
| 450 | 2 | | 2 | 59 | 7 | 11.9 | 55 | 54 | 3.7 |
| 480 | | | | 58 | 7 | 11.9 | 51 | 51 | |
| 510 | 1 | | | 58 | 8 | 13.8 | 51 | 51 | 2.0 |
| 540 | 2 | 1 | 1 | 57.5 | 10 | 17.4 | 50 | 49 | 4.1 |
| 570 | | | | 57 | 10 | 17.4 | 46 | 46 | |
| 600 | 2 | | | | 12 | 21.0 | 46 | 46 | 4.3 |
| 630 | 2 | | | | 14 | 24.6 | 44 | 44 | 4.5 |
| 660 | 2 | 1 | | | 16 | 28.1 | 42 | 41.5 | 4.8 |
| 690 | 4 | 1 | 1 | 56.5 | 20 | 35.4 | 39 | 38 | 10.5 |
| 720 | 5 | 1 | | 56 | 25 | 44.6 | 33 | 32.5 | 15.4 |
| 750 | 2 | 3 | 4 | 54 | 27 | 50.0 | 27 | 23.5 | 8.5 |
| 780 | 4 | 1 | 1 | 51.5 | 31 | 60.2 | 18 | 17 | 23.5 |
| 810 | 1 | 4 | 2 | 50 | 32 | 64.0 | 12 | 9 | 11.1 |
| 840 | | | | 49 | 32 | 64.0 | 5 | 5 | |
| 870 | 2 | 1 | | | 34 | 69.4 | 5 | 4.5 | 44.4 |
| 900 | 2 | | | | 36 | 73.5 | 2 | 2 | 100.0 |

Appendix

Table 7. Life table, Lot 14 (part 2).

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT rat-month |
| 300-330 | | | | 61 | | | 61 | 61 | |
| 360 | 1 | | | 61 | 1 | 1.6 | 61 | 61 | 1.6 |
| 390 | 2 | | 1 | 60.5 | 3 | 4.9 | 60 | 59.5 | 3.4 |
| 420 | | 1 | | 60 | 3 | 4.9 | 57 | 56.5 | |
| 450 | 1 | | | | 4 | 6.7 | 56 | 56 | 1.8 |
| 480 | | 1 | | | 5 | 6.7 | 55 | 54.5 | |
| 510 | 2 | 2 | | | 6 | 10.0 | 54 | 53 | 3.8 |
| 540 | 1 | 2 | | | 7 | 11.7 | 50 | 49 | 2.0 |
| 570 | 4 | | | | 11 | 18.3 | 47 | 47 | 8.5 |
| 600 | 2 | | | | 13 | 21.7 | 43 | 43 | 4.7 |
| 630 | 2 | 1 | | | 15 | 25.0 | 41 | 40.5 | 4.9 |
| 660 | 4 | 2 | 2 | 59 | 19 | 32.2 | 38 | 36 | 11.1 |
| 690 | 5 | 1 | 1 | 57.5 | 24 | 41.7 | 30 | 29 | 17.2 |
| 720 | 6 | | | 57 | 30 | 52.6 | 23 | 23 | 26.1 |
| 750 | 1 | 2 | | | 31 | 54.4 | 17 | 16 | 6.2 |
| 780 | 3 | | | | 34 | 59.6 | 14 | 14 | 21.4 |
| 810 | 2 | 3 | | | 36 | 63.1 | 11 | 9.5 | 21.0 |
| 840 | | | | | 36 | 63.1 | 6 | 6 | |
| 870 | 1 | 1 | | | 37 | 64.9 | 6 | 5.5 | 18.2 |
| 900 | | 1 | | | 37 | 64.9 | 4 | 3.5 | |
| 930 | | 1 | | | 37 | 64.9 | 3 | 2.5 | |
| 960 | 1 | 1 | | | 38 | 66.7 | 2 | 1.5 | 66.7 |

Appendix

Table 8. Life table, Lot 14.

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT rat-month |
| L300 | 2 | | | 121 | 2 | 1.6 | 121 | 121 | |
| 300-330 | 1 | | | 121 | 3 | 2.5 | 119 | 119 | 0.8 |
| 360 | 2 | | | 121 | 5 | 4.1 | 118 | 118 | 1.7 |
| 390 | 1 | | 1 | 120.5 | 6 | 5.0 | 116 | 115.5 | 0.9 |
| 420 | 1 | 1 | | 120 | 7 | 5.8 | 113 | 112.5 | 0.9 |
| 450 | 3 | | 2 | 119 | 10 | 8.4 | 111 | 110 | 2.7 |
| 480 | | 1 | | 118 | 10 | 8.5 | 106 | 105.5 | |
| 510 | 3 | 2 | | 118 | 13 | 11.0 | 105 | 104 | 2.9 |
| 540 | 3 | 3 | 1 | 117.5 | 16 | 13.6 | 100 | 98 | 3.1 |
| 570 | 4 | | | 117 | 20 | 17.1 | 93 | 93 | 4.3 |
| 600 | 4 | | | 117 | 24 | 20.5 | 89 | 89 | 4.5 |
| 630 | 4 | 1 | | 117 | 28 | 23.9 | 85 | 84.5 | 4.7 |
| 660 | 6 | 3 | 2 | 116 | 34 | 29.3 | 80 | 77.5 | 7.7 |
| 690 | 9 | 2 | 2 | 114 | 43 | 37.7 | 69 | 67 | 13.4 |
| 720 | 11 | 1 | | 113 | 54 | 47.7 | 56 | 55.5 | 19.8 |
| 750 | 3 | 5 | 4 | 111 | 57 | 51.2 | 44 | 39.5 | 7.6 |
| 780 | 7 | 1 | 1 | 108.5 | 64 | 59.0 | 32 | 31 | 22.6 |
| 810 | 3 | 7 | 2 | 107 | 67 | 62.6 | 23 | 18.5 | 16.2 |
| 840 | | | | 106 | 67 | 63.2 | 11 | 11 | |
| 870 | 3 | 2 | | ↓ | 70 | 66.0 | 11 | 10 | 30.0 |
| 900 | 2 | 1 | | | 72 | 67.9 | 6 | 5.5 | 36.3 |
| 930 | 1 | 1 | | | 73 | 68.9 | 3 | 2.5 | 40.0 |
| 960 | 1 | 1 | | ↓ | 74 | 69.8 | 2 | 1.5 | 66.7 |

Appendix

Table 9. Life table, Lot 17.

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT rat-month |
| 300-330 | 2 | | | 84 | 2 | 2.4 | 84 | 84 | 2.4 |
| 360 | 1 | | | | 3 | 3.6 | 82 | 82 | 1.2 |
| 390 | 1 | | | | 4 | 4.8 | 81 | 81 | 1.2 |
| 420 | 3 | 2 | | | 7 | 8.3 | 80 | 79 | 3.8 |
| 450 | 1 | 4 | | | 8 | 9.5 | 75 | 73 | 1.4 |
| 480 | 3 | | | | 11 | 13.1 | 70 | 70 | 4.3 |
| 510 | 2 | 2 | 1 | 83.5 | 13 | 15.6 | 67 | 65.5 | 3.1 |
| 540 | 3 | 1 | | 83 | 16 | 19.3 | 62 | 61.5 | 4.9 |
| 570 | 3 | 8 | | | 19 | 22.9 | 58 | 54 | 5.6 |
| 600 | 5 | 1 | | | 24 | 28.9 | 47 | 46.5 | 10.8 |
| 630 | 4 | 8 | | | 28 | 33.7 | 41 | 37 | 10.8 |
| 660 | 3 | 1 | 1 | 82.5 | 31 | 37.6 | 29 | 28 | 10.7 |
| 690 | 1 | | | 82 | 32 | 39.0 | 24 | 24 | 4.2 |
| | | | | | | | 23 | 23 | still living |

Appendix

Table 10. Life table, all Charles River "COBS" controls.

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT rat-month |
| L300 | 4 | | | | | | 435 | 435 | |
| 300 | 6 | | | 435 | 10 | 2.3 | 431 | 431 | 1.4 |
| 360 | 5 | | | 435 | 15 | 3.4 | 425 | 425 | 1.2 |
| 390 | 3 | | 5 | 433.5 | 18 | 4.2 | 420 | 417.5 | 0.7 |
| 420 | 5 | 3 | 6 | 431 | 23 | 5.3 | 412 | 407.5 | 1.2 |
| 450 | 8 | 6 | 6 | 421 | 31 | 7.4 | 398 | 392 | 2.0 |
| 480 | 7 | 3 | 5 | 415.5 | 38 | 9.1 | 378 | 374 | 1.9 |
| 510 | 10 | 7 | 1 | 412.5 | 49 | 11.9 | 363 | 359 | 2.8 |
| 540 | 18 | 7 | 4 | 410 | 67 | 16.3 | 345 | 339.5 | 5.3 |
| 570 | 14 | 13 | 1 | 407.5 | 81 | 19.9 | 316 | 309 | 4.5 |
| 600 | 22 | 5 | | 407 | 103 | 25.3 | 288 | 285.5 | 7.7 |
| 630 | 13 | 13 | 2 | 406 | 116 | 28.6 | 261 | 253.5 | 5.1 |
| 660 | 19 | 9 | 6 | 402 | 135 | 33.6 | 233 | 225.5 | 8.4 |
| 690 | 21 | 6 | 3 | 397.5 | 156 | 39.2 | 199 | 194.5 | 10.8 |
| 720 | 19 | 7 | 2 | 372 | 175 | 47.0 | 146* | 141.5 | 13.4 |
| 750 | 10 | 7 | 4 | 369 | 185 | 50.1 | 118 | 112.5 | 8.9 |
| 780 | 13 | 5 | 1 | ↓ | 198 | 53.6 | 97 | 94 | 13.8 |
| 810 | 6 | 9 | 2 | ↓ | 204 | 55.6 | 78 | 72.5 | 8.3 |
| 840 | 9 | 3 | | 367 | 213 | 58.0 | 61 | 59.5 | 15.1 |
| 870 | 12 | 6 | | ↓ | 225 | 61.3 | 49 | 46 | 26.1 |
| 900 | 11 | 5 | | ↓ | 236 | 64.3 | 31 | 28.5 | 38.6 |
| 930 | 3 | 2 | | ↓ | 239 | 65.1 | 15 | 14 | 21.4 |
| 960 | 2 | 2 | | ↓ | 241 | 65.7 | 10 | 9 | 22.2 |
| 990 | 0 | 2 | | ↓ | 241 | 65.7 | 6 | 5 | |
| 1020 | 2 | 2 | | ↓ | 243 | 66.2 | 4 | 3 | 66.7 |

*23 rats of Lot 17 still living.

Appendix

Table 11. Life table, Lot A ($F_1$ of Lot 1).

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT / rat-month |
| 300-330 | | | | 60 | | | 60 | 60 | |
| 360 | | | | | | | 60 | 60 | |
| 390 | | | 5 | | | | 60 | 57.5 | |
| 420 | 1 | | | 55 | 1 | 1.8 | 55 | 55 | 1.8 |
| 450 | | | | | 1 | 1.8 | 54 | 54 | |
| 480 | | | | | 1 | 1.8 | 54 | 54 | |
| 510 | 1 | | | | 2 | 3.6 | 54 | 54 | 1.9 |
| 540 | 1 | | | | 3 | 5.4 | 53 | 53 | 1.9 |
| 570 | 4 | 1 | | | 7 | 12.7 | 52 | 51.5 | 7.8 |
| 600 | | 1 | 2 | 54 | 7 | 12.7 | 47 | 45.5 | |
| 630 | 3 | 1 | | 53 | 10 | 18.8 | 44 | 43.5 | 6.9 |
| 660 | 2 | | | 53 | 12 | 22.6 | 40 | 40 | 5.0 |
| 690 | 1 | 3 | 1 | 52.5 | 13 | 24.8 | 38 | 36 | 2.8 |
| 720 | 5 | | | 52 | 18 | 34.6 | 33 | 33 | 15.1 |
| 750 | 2 | 1 | | | 20 | 38.5 | 28 | 27.5 | 7.3 |
| 780 | 3 | 1 | | | 23 | 44.2 | 25 | 24.5 | 12.2 |
| 810 | 2 | 1 | | | 25 | 48.1 | 21 | 20.5 | 9.8 |
| 840 | | 2 | | | 25 | 48.1 | 18 | 17 | |
| 870 | 3 | 1 | | | 28 | 53.8 | 16 | 15.5 | 19.4 |
| 900 | 3 | 1 | | | 31 | 59.6 | 12 | 11.5 | 26.1 |
| 930 | 1 | | | | 32 | 61.5 | 8 | 8 | 12.5 |
| 960 | 1 | | | | 33 | 63.5 | 7 | 7 | 14.3 |
| 990 | 1 | | | | 34 | 65.4 | 6 | 6 | 16.7 |
| 1020 | 1 | | | | 35 | 67.3 | 5 | 5 | 20.0 |
| 1050 | | 4 | | | | | 4 | 4 | |

Appendix

Table 12. Life table, uniparous (Lot 15).

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT rat-month |
| 300-330 | 1 | | | 53 | 1 | 1.9 | 53 | 53 | 1.9 |
| 360 | | | | 53 | 1 | 1.9 | 52 | 52 | |
| 390 | | | | 53 | 1 | 1.9 | 52 | 52 | |
| 420 | | | 1 | 52.5 | 1 | 1.9 | 52 | 51.5 | |
| 450 | 2 | | 1 | 51.5 | 3 | 5.8 | 51 | 50.5 | 4.0 |
| 480 | 2 | | | 51 | 5 | 9.8 | 48 | 48 | 4.2 |
| 510 | | | 1 | 50.5 | 5 | 9.8 | 46 | 45.5 | |
| 540 | | 1 | | 50 | 5 | 9.8 | 45 | 44.5 | |
| 570 | 2 | 3 | | 50 | 7 | 14.0 | 44 | 41.5 | 4.8 |
| 600 | 2 | | 1 | 49.5 | 9 | 18.2 | 39 | 38.5 | 5.2 |
| 630 | | | | 49 | 9 | 18.2 | 36 | 36 | |
| 660 | 2 | 1 | | 49 | 11 | 22.4 | 36 | 35.5 | 5.6 |
| 690 | 2 | 1 | | 49 | 13 | 26.5 | 33 | 32.5 | 6.2 |
| 720 | 3 | 1 | 1 | 48.5 | 16 | 33.0 | 30 | 29 | 10.3 |
| 750 | 1 | | 5 | 45.5 | 17 | 37.4 | 25 | 22.5 | 4.4 |
| 780 | 2 | | 2 | 42 | 19 | 45.2 | 19 | 18 | 11.1 |
| 810 | 1 | 1 | 1 | 40.5 | 20 | 49.4 | 15 | 14 | 7.1 |
| 840 | 3 | 1 | | 40 | 23 | 57.5 | 12 | 11.5 | 25.0 |
| 870 | | | | | 23 | 57.5 | 8 | 8 | |
| 900 | 1 | 1 | | | 24 | 60.0 | 8 | 7.5 | 13.3 |
| 930 | 3 | 2 | | | 27 | 67.5 | 6 | 5 | 60.0 |
| 960 | 1 | | | | 28 | 70.0 | 1 | 1 | 100 |

Appendix

Table 13. Life table, thyroidectomized (Lot 1).

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| Interval | MT | Deaths | Extran. deaths | Corr. pop. | Cum. MT | % Cum. MT | Pop. at start | Rats at risk for month | % MT / rat-month |
| 300-330 | 1 | | | 45 | 1 | 2.2 | 45 | 45 | 2.2 |
| 360 | | | | | 1 | 2.2 | 44 | 44 | |
| 390 | | | | | 1 | 2.2 | 44 | 44 | |
| 420 | 1 | 1 | | | 2 | 4.4 | 44 | 43.5 | 2.3 |
| 450 | | | | | 2 | 4.4 | 42 | 42 | |
| 480 | | | | | 2 | 4.4 | 42 | 42 | |
| 510 | 1 | | | | 3 | 6.7 | 42 | 42 | 2.4 |
| 540 | 1 | 1 | | | 4 | 8.9 | 41 | 40.5 | 2.5 |
| 570 | | | | | 4 | 8.9 | 39 | 39 | |
| 600 | 2 | | | | 6 | 13.3 | 39 | 39 | 5.1 |
| 630 | 1 | 1 | | | 7 | 15.5 | 37 | 36.5 | 2.7 |
| 660 | 2 | 1 | | | 9 | 19.9 | 35 | 34.5 | 5.8 |
| 690 | 2 | 2 | | | 11 | 24.4 | 32 | 31 | 6.5 |
| 720 | 1 | 1 | | | 12 | 26.7 | 28 | 27.5 | 3.6 |
| 750 | 2 | | | | 14 | 31.1 | 26 | 26 | 7.7 |
| 780 | 1 | 1 | | | 15 | 33.3 | 24 | 23.5 | 4.3 |
| 810 | 7 | | | | 22 | 48.9 | 22 | 22 | 31.8 |
| 840 | 3 | | | | 25 | 55.6 | 15 | 15 | 20.0 |
| 870 | | 1 | | | 25 | 55.6 | 12 | 11.5 | |
| 900 | 2 | | | | 27 | 60.0 | 11 | 11 | 18.2 |
| 930 | | 2 | | | 27 | 60.0 | 9 | 8 | |
| 960 | 2 | | | | 29 | 64.4 | 7 | 7 | 28.6 |
| 990 | | | | | 29 | 64.4 | 5 | 5 | |
| 1020 | 1 | 1 | | | 30 | 66.7 | 5 | 4.5 | 22.2 |
| 1050 | 1 | | | | 31 | 68.9 | 3 | 3 | 33.3 |
| 1080 | | | | | 31 | 68.9 | 2 | 2 | |
| 1110 | | | | | 31 | 68.9 | 2 | 2 | |
| 1140 | | | | | 31 | 68.9 | 2 | 2 | |
| 1170 | 1 | 1 | | | 32 | 71.1 | 2 | 1.5 | 66.7 |

Appendix

Table 14. Life table, ovariectomized (Lot 1).

| 1 Interval | 2 MT | 3 Deaths | 4 Extran. deaths | 5 Corr. pop. | 6 Cum. MT | 7 % Cum. MT | 8 Pop. at start | 9 Rats at risk for month | 10 % MT / rat-month |
|---|---|---|---|---|---|---|---|---|---|
| 570-600 | | 1 | | 45 | | | 45 | 44.5 | |
| 630 | | | | | | | 44 | 44 | |
| 660 | 1 | 3 | | | 1 | 2.2 | 44 | 42.5 | 2.4 |
| 690 | | 1 | | | | | 40 | 39.5 | |
| 720 | | 1 | | | | | 39 | 38.5 | |
| 750 | | 1 | | | | | 38 | 37.5 | |
| 780 | | | | | | | 37 | 37 | |
| 810 | | 2 | | | | | 37 | 36 | |
| 840 | | 1 | | | | | 35 | 34.5 | |
| 870 | | 2 | | | | | 34 | 33 | |
| 900 | | 1 | | | | | 32 | 31.5 | |
| 930 | 1 | | | | 2 | 4.4 | 31 | 31 | 3.2 |
| 960 | | 3 | | | | | 30 | 28.5 | |
| 990 | 1 | 3 | | | 3 | 6.7 | 27 | 25.5 | 3.9 |
| 1020 | | 3 | | | | | 23 | 21.5 | |
| 1050 | | 5 | | | | | 20 | 17.5 | |
| 1080 | | 2 | | | | | 15 | 14 | |
| 1110 | | 1 | | | | | 13 | 12.5 | |
| 1140 | | 4 | | | | | 12 | 10 | |
| 1170 | | 6 | | | | | 8 | 5 | |
| 1200 | | | | | | | 2 | 2 | |
| 1230 | | | | | | | 2 | 2 | |
| 1260 | | | | | | | 2 | 2 | |
| 1290 | | | | | | | 2 | 2 | |
| 1320 | | 2 | | | | | 2 | 2 | |