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Possible Effect of Oil of Gaultheria in Diet of Mice Susceptible to Spontaneous Carcinoma of the Breast. I. A Suggestion.

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The present experiment dealing with the addition of small traces of oil of gaultheria (true wintergreen oil) to the otherwise normal diet of mice, has given some interesting data. The mice used were individuals belonging to a highly inbred stock (the D strain). This stock is a branch of the dilute brown strain which has an unbroken line, mainly of brother-to-sister descent, extending over 25 years (Little and Murray). The inbreeding was initiated by Little and the stock is usually referred to as the Little Dilute Browns. My branch had passed through several individual laboratories before coming into my own. At present my dilute brown stock is in the tenth generation of pedigreed brother-to-sister matings.

Breeding females of this stock are very prone to develop spontaneous adeno-carcinoma of the breast. Murray, who has made more observations on the incidence of neoplasia in individuals of this stock than anyone else, has found more than 1300 spontaneous tumors in the past 5 years. Of all the female mice which are used as breeders, fully 80% develop carcinoma. The common infections are the cause of death of the remaining 20%. It is Murray's opinion that if all breeding females of this stock would live long enough they would all develop carcinoma of the breast.

My sub-line shows parallel findings, differing only in minor details. Whereas Murray reports 1300 spontaneous tumors, I have had only 115. This is due to the fact that individuals of other stocks in my laboratory have been better breeders and consequently have filled up most of my available cages. The incidence of spontaneous tumors in the individuals, however, is as high as it has been in the Murray derivatives of the dilute browns. If only mice that live beyond the 8 month period (when the "cancer" age is just manifesting itself) are included, then 75% of my breeding females have developed breast carcinoma. In the second place, the age at which my breeding females develop breast carcinoma is slightly later in life than those in Murray's laboratory. The mean age at which

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Murray's female mice develop breast carcinoma is between 10 and 11 months, whereas the value for my stock is at 12 months.

The diet on which my mice had been kept for the past 7 years consists of rolled oats, meat scrap, powdered skim milk, salt, water and Old Grist Mill dog biscuit. The first 4 items were thoroughly mixed together in the following proportion: rolled oats 90 lb., meat scrap 5 qt., powdered milk 8 qt., salt 1 lb.

The water was given in a regular 16 oz. bottle with a glass tubing drawn out to a small bore. Food and water were available to the mice at all times.

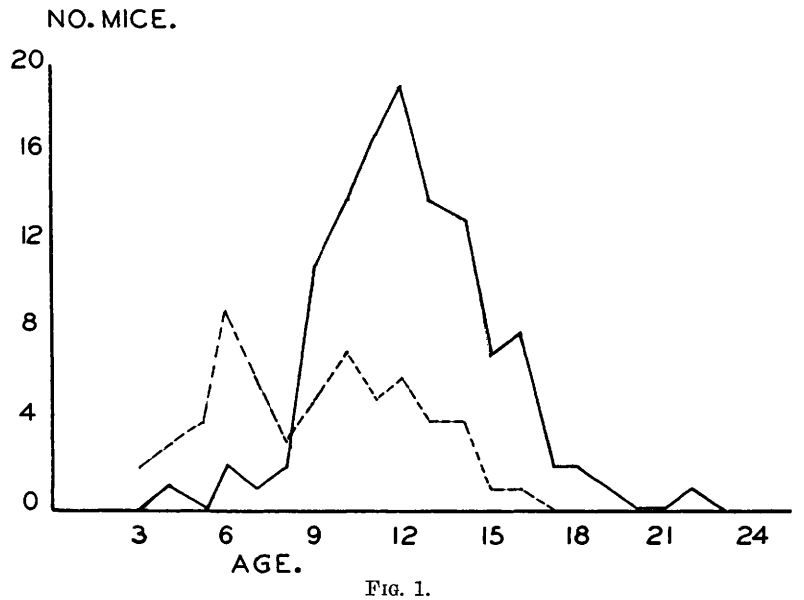

FIG. 1.

The age distribution of (1) mice developing carcinoma of the breast (solid line) and (2) the age mortality curve for all other causes of death than cancer (dash line). All mice included in this figure were kept on the normal oat meal (control) diet.

Fig. 1 shows (1) the age distribution of carcinoma and (2) the mortality curve of all other causes of death than cancer obtained with normal breeding females on the normal diet given above.

It will be noted, (1) mice of this stock go through a period of depression (as measured by the height of the mortality curve) at 6 months of age, (2) if the mice recover from this period of depression they develop carcinoma of the breast in the great majority of cases, (3) mice dying of other causes than cancer have all died by 17 months, (4) the age distribution of breast carcinoma presents a fair unimodal curve considering that only 115 cases are recorded,

and (5) the oldest mouse in this stock developed carcinoma of the breast at 22 months. The average age of mice dying of all other causes than cancer is 8.9 months.

February 26, 1932, and the subsequent 6 days, I started 45 individuals that had been used for breeders on the above rolled oat diet to which had been added small amounts of oil of gaultheria. These mice averaged 11.7 months of age. The breeding was discontinued from that time on. For 41 days, one drop of the oil was added to 10 gm. of the rolled oat diet; then for 26 days one drop of oil to 50 gm. of the rolled oat diet was given; and finally one drop to 40 gm. has been continued to the end of the experiment. No dog biscuit was given while the mice were on the oil-treated rolled oat diet.

Fig. 2 presents the data obtained.

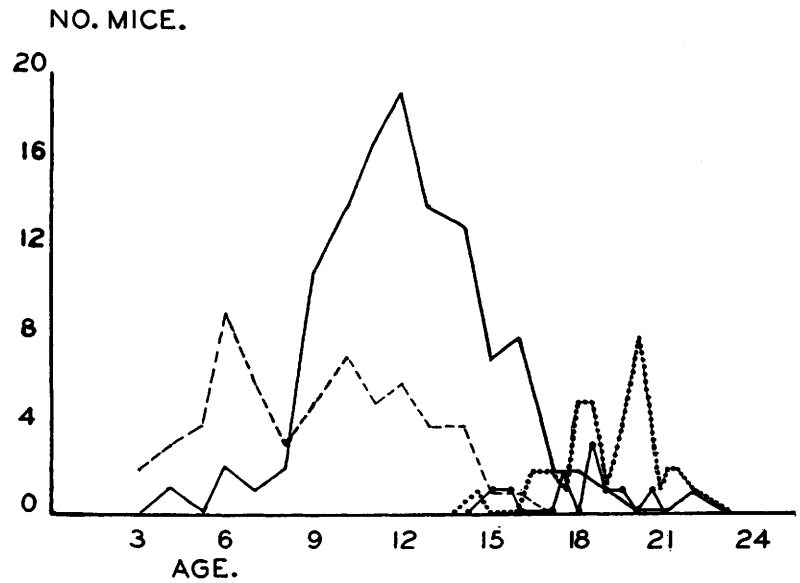

FIG. 2.

The same data as in Fig. 1 and data obtained with the oil gaultheria—rolled oat diet. The chart shows 4 classes of mice: (1) the age distribution for mice developing carcinoma of the breast on the control diet (solid line), (2) the mortality curve for mice dying from all other causes than cancer (on control oat meal diet) (dash line), (3) the age distribution for the mice that developed carcinoma of the breast on the oil gaultheria—oat meal diet (solid and ball line), and (4) the mortality curve for all other causes of death than cancer obtained with mice on the oil gaultheria—rolled oat diet (dotted line).

Ten mice of the original 45 individuals placed on the oil gaultheria diet developed spontaneous tumors. Their ages averaged 18.0 months, whereas the average for the mice on the control diet was 12.1 months. Thirty-five of the original 45 mice died of other

causes than cancer at ages beyond the time the control mice had normally developed carcinoma (average 19 months).

The experimental animals had received 2 influences other than the oil-gaultheria diet at the time of the experiment: (1) the animals were no longer used as breeders, and (2) dog biscuit had been dropped from their diet. It has been ascertained by Murray[1] that there is no difference in the cancer rate between mice that have had one litter and those that have had several. There is a real difference between virgin females and those that have been used for breeders. At no other stage in the life history of mice is there any reproductive factor that has been recognized as a disturbing element in the rate at which cancer develops. All mice used in this experiment had been used for breeders. They were placed in reserve merely to simplify their physiological behavior. Murray[2] has also shown that for the stock of mice I used the cessation of the mice from breeding does not influence either the age distribution of spontaneous carcinoma of the breast or the expectancy of life. As to discontinuing dog biscuit in the diet, several times in the past the type of dog biscuit and other food elements have been changed without any apparent effect on the cancer rate.

I realize the following limitations of the present data: (1) the number of mice used, (2) late age period for placing the mice on an experimental diet, and (3) problematical validity of the control group. These criticisms are being more carefully considered in subsequent papers in this series.

It is therefore possible that by the addition of small amounts of oil of gaultheria to the control diet, one may delay the time at which breast carcinoma would normally develop.

This finding would be quite valueless if by obtaining it the normal physiology of the individual was in any way impaired. The first effect noted was that the experimental mice ate more food than the controls. This finding verifies the work of Wiley.[3] The experimental animals did not become obese as normal mice kept in reserve from males are apt to do. Daily weights of the mice were not kept so it is impossible to determine whether the experimental animals actually lost weight. The fact that the experimental mice lived longer than the controls is presumptive evidence that they were not physiologically weakened by the special diet. The common causes

[1] Murray, W. S., unpublished data by oral communication.

[2] Murray, W. S., *Science*, 1932, **75**, 646.

[3] Wiley, H. W., Salicyl, U. S. Bur. Chem., Circ. N. 84, 1906, cited by Sollman. Manual of Pharmacology.

of death were the same as for the controls (1) pneumonia, (2) paratyphoid, (3) sarcosporidia infection, and (4) nephritis.

Whether or not any of the known facts concerning the effect of oil of gaultheria over a long period on the physiology of the organism can explain this delay in the age incidence of carcinoma is problematical. At least certain effects of this oil may be significant.

Oil of gaultheria, in common with some other salicylates,[4, 5] retards enzymic activity, especially of the digestive enzymes. According to some observers basal metabolism is elevated in patients suffering with carcinoma.[6] Is there a disturbance of basal metabolism in the earliest stages of carcinoma? Is it possible for this disturbance to be present even before cancer is obvious? Does the addition of oil of gaultheria to the diet correct this variation of basal metabolism and so exert an influence on the age incidence of cancer? These problems require more research.

These observations are being repeated on several distinct stocks of mice. At the same time the experiments call for further investigation. Is oil of gaultheria unique in this possible respect of delaying the incidence of cancer, or are other essential oils, especially those used in food flavoring, comparable? This problem is being investigated. The second problem is the effect of administration of the essential oils used in food flavoring (especially oil of gaultheria) on younger animals. It is hoped that perhaps the time at which cancer normally develops may be thus indefinitely postponed.

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Functional Sites in Normal and Segmentally Necrotic Renal Tubules.

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Intraperitoneal or lymph sac (frog) injections of 1% solutions of ferric ammonium citrate and sodium ferrocyanide were made in 50 rats, 10 turtles and 100 frogs. The presence of either salt or both in the kidney of these animals, depending on whether one or the

[4] Bastedo, Materia Medica, Pharmacology and Therapeutics, 3rd Ed., 1932.

[5] Cushny's Pharmacology and Therapeutics, 9th edition, 1928.

[6] Palmer, Walter W., Metabolism, Chapter 2, Vol. 3, *Nelson's Loose-Leaf Living Medicine,* November, 1926.