

Extensive Breeding as an Adjunct to Mammary Gland Carcinoma Susceptibility in Mice.

LEONELL C. STRONG.*

From the Department of Anatomy, Yale University School of Medicine.

Susceptibility to carcinoma of the mammary gland in mice of the F_1 generation, following an outcross, is usually determined by the female parent, that is, if a female mouse of a cancer susceptible strain be used in an outcross to a male mouse of a resistant-to-cancer strain the F_1 females develop spontaneous tumors; whereas, if the reverse cross be made, female mice of the F_1 generation do not usually develop spontaneous tumors of mammary tissue. It is Bittner's opinion that the "milk influence" explains this peculiar maternal inheritance of cancer susceptibility. The "forced breeding" principle of Bagg also plays a role in cancer susceptibility but apparently only upon a suitable genetic background.

In the present experiment, consisting of 2 parts, female mice of the JK strain (cancer resistant) were mated to male mice of the C_3H strain (cancer susceptible). The ensuing F_1 individuals were mated either *inter se* or back-crossed to either mice of the original C_3H or JK strains. Mice were continued as breeders for their entire life span, the sexes being kept together. This procedure differs from the "forced breeding" technic of Bagg in that the mice were permitted to nurse their own young, whereas in "forced breeding" the young were discarded within 24 hours of birth. The cyclic changes within the mammary gland are considerably different therefore in the two systems of breeding. Following sexual maturity, the female mice were kept, in this experiment, in an almost continuous reproductive activity—nursing one litter while the next one was developing *in utero*. This regime was greatly aided by maximal nutritional conditions. This reproductive activity was also enhanced by the fact that F_1 individuals show the phenom-

enon of heterosis, which influences health and vigor of mice as well as of other animals and plants. The mice were fed a diet of Pratt Food Company's Nurishmix, supplemented (a) by fresh washed lettuce twice a week; (b) by fortified or vitamin enriched Bond bread soaked in fresh milk once a week; and (c) by a mixture of 2 parts of oats to one part of wheat twice a week. Water was supplied *ad lib*. Thus conditions for the extensive use of the mice as breeders were satisfied. Seventeen of the 24 F_1 females, with mothers of the JK strain, eventually developed spontaneous carcinoma of the mammary gland at an average of 476.2 days of life. In the reverse cross, 25 of the 30 F_1 females with C_3H mothers developed similar tumors at an average age of 424.6 days. The difference of susceptibility between the 2 F_1 female groups is probably not a significant one.

Thus it would seem that the extensive or excessive use of female mice of the F_1 generation, in this particular cross, between mice of the C_3H and JK strains is an effective way of bringing about spontaneous tumors of mammary tissue. The genetic factor of cancer susceptibility could only have been transmitted through the male. The role of the "milk influence," in this case, is not clear.

In the sequence of events that leads to susceptibility or resistance to spontaneous tumors of mammary origin, there appear to be at present many influences. Among these may be (1) genetic (2) hormonal (3) chemical (4) dietary and (5) normal and abnormal uses such as "forced breeding," and extensive use. As indicated in this paper the role of each of these influences appears to differ considerably under different experimental set-ups. Some of these influences appear to be cumulative in effect, such as the genetic and hormonal; some, such as the chemical and genetic, appear to be supple-

* This experiment has been made possible by grants from The Jane Coffin Childs Memorial Fund for Medical Research and The Anna Fuller Fund.

mentary or alternative. It may be that in this phenomenon of cancer susceptibility there may be still another influence, whose nature is not yet determined, that is also

involved in the origin of tumors. Some geneticists believe that this may be in the form of a somatic mutation.

14273

Influence of Spinal Section on Tissue Permeability.*

F. HOMBURGER.[†] (Introduced by F. Duran-Reynals.)

From the Laboratory of Pathology, Yale University School of Medicine, New Haven, Conn.

The experiments reported here were designed to determine the effect on tissue permeability of transections of the spinal cord at levels varying from the first to the fifth thoracic segment. The spreading of india ink suspensions in the cutaneous connective tissue was used as indicating the degree of connective tissue permeability. Tissue permeability measured in this way is affected by constitutional, nutritional and functional conditions and by the spreading factors (Duran-Reynals)¹ but no influence of the nervous system has been demonstrated. McClean's² results, obtained in excised skin, were interpreted as indicating that spreading is independent of vasomotor or other nervous stimuli.

The present study was designed to determine whether or not the nervous system is involved in the regulation of tissue permeability in living animals.

Materials and Methods. Twelve animals (11 rabbits and 1 dog) were used as follows:

India ink with saline and india ink with spreading factor[†] were injected into the skin of the upper and lower part of one side of the animal's body. Twenty-four hours later the extent of spread of the ink spots was recorded by drawing the areas on cellophane and measuring their surfaces in square centimeters with a planimeter.

The spinal cord was then completely transected under local anesthesia at levels varying from the first to the fifth thoracic segment.

Following operation injections of identical amounts of the same mixtures of india ink and saline and of india ink and spreading factor were repeated on the opposite side of the animal's body, care being taken to select injection sites comparable to those used before operation. This was repeated after 24 hours and every subsequent day until all available skin surface was used (usually 3 to 7 days). Twenty-four hours after injection the spread of india ink was traced and measured in the manner indicated above.

For purposes of control 3 animals were laminectomized without spinal cord injury and treated similarly.

All animals were kept in a warm box at 35°C after operation to prevent loss of body heat. Repeated blood pressure readings were taken before and after operation. In all instances the central ear artery was utilized and the blood pressure as determined by oscillometric methods showed constant variations ranging between 65 mm Hg and 95 mm Hg before and after operation.

The spinal animals developed paralysis of the hind legs, urinary bladder and rectal sphincter and in several instances ataxia of

* This work was aided by a grant from the Commonwealth Fund.

[†] With the technical assistance of Alvin R. Nielsen.

¹ Duran-Reynals, F., *Bacteriological Reviews*, 1942, **4**, 197.

² McClean, D., *J. Path. Bact.*, 1931, **34**, 459.

[†] India ink (Higgins) was used, diluted in equal parts of saline. All injections contained 0.25 cc of this suspension. The saline injections contained in addition 0.5 cc of physiological NaCl solution. The injections of spreading factor contained 0.5 cc of leech extract in saline 1:10 or extract of rats' testicles in saline 1:10 (0.5 cc). This material was supplied by Dr. Duran-Reynals whose help and advice are deeply appreciated.