UNUSUAL PROLIFERATION OF BILE-DUCT CELLS IN ICR FEMALE MICE GIVEN 2,7-FLUORENYLBISACETAMIDE WHILE NURSING SUCKLINGS

This study was primarily aimed to seek evidence, if any, of age factors which might influence tumor development, either qualitatively or quantitatively, when the test animals were exposed to 2,7-fluorenylbisacetamide (2,7-FAA) in diet, and the present communication deals with the result that ICR female mice which were nursing their sucklings showed unique susceptibility to unusual proliferation of bile-duct cells when given a feed containing 2,7-FAA.

ICR mice were divided into the following 5 groups by the age of the animals when the administration of the carcinogen started. Group 1: Mother mice 7 days after delivery and nursing their litter. Group 2: Seven-day-old suckling mice of both sexes, which were being nursed by the mice of Group 1. Group 3: Virgin mice of both sexes, 50 days of age. Group 4: Virgin mice of both sexes, 7 months of age, which had been given a single subcutaneous injection of 2,7-FAA (0.5 mg) at birth. Group 5: Virgin mice of both sexes, 10 months of age.

The animals were all fed on a basal diet (Oriental NMF) supplemented with 0.025% 2,7-FAA. They were given water and the experimental diet freely. The mice in Group 2 were weaned at about 4 weeks of age. The experimental animals of Groups 1, 4, and 5 were autopsied 2 months after the initiation of 2,7-FAA administration. The mice in Groups 2 and 3 were killed 2, 3, 4, 6, or 9 months after initiation of the carcinogen administration.

The body weight of the mice in Groups 2 to 5 tended to decrease or showed a delay in growth for the first 2 or 3 weeks after the initiation of 2,7-FAA administration and was followed by gradual recovery. These mice could be kept for 6 months or more till the malignant tumors were induced in their organs. On the other hand, most of the mice in Group 1 could not be kept alive longer than 2 months.

When the animals were autopsied 2 months after the initiation of 2,7-FAA administration, 9 out of 20 mice in Group 1 had nodular or color-changed lesions in multiple sites in their liver. The size of the lesions was mostly less than 2 mm in diameter. Five out of the nine mice also had accumulation of ascites fluid. Microscopic examination revealed that majority of the lesions was a nest of cholangiomatous proliferation of mature bile-duct cells of cylindrical shape. In a few cases, the lesions were a nodular hyperplasia of hepatocytes. In addition to these findings, remarkable proliferation of oval-shaped cells, which have been identified as immature bile-duct cells,1,2) was also seen throughout these livers. In 19 out of 20 mice in Group 1, proliferation of bile-duct cells was so remarkable that the architecture of liver lobules was obscured due to the infiltration of oval-shaped cells into almost all regions of the liver and/or due to the growth of mature bile-duct cells in cholangiomatous pattern.

On the contrary, none of the mice in Groups 2 to 5, which were autopsied at the same period of the 2,7-FAA administration (12 females in Group 1, 6 females and 11 males in Group 2, 11 females and 11 males in Group 3, and 6 females and 6 males in Group 4), showed such remarkable findings. However, a relatively slight degree of proliferation of immature bile-duct cells of oval-shape was occasionally seen in some female
mice in these Groups. The mice Groups 2 and 3, which were autopsied 3 or 4 months after the initiation of the carcinogen administration, also showed proliferation of bileduct cells, but its degree was not so remarkable as those in the mice of Group 1.

These data suggest that the susceptibility of the cells of the liver to 2,7-FAA or the metabolism of 2,7-FAA is possibly influenced by complex phenomena accompanying physiological conditions such as pregnancy, delivery, or nursing of the test animals.

The experimental evidence on the problem of age factors relating to 2,7-FAA carcinogenesis will be reported in detail later.

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REFERENCES