EFFECT OF BIOMYCIN ON INDUCTION OF LIVER TUMORS IN MICE

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Biomycin, if injected into mice in the early stages of carcinogenesis due to o-amino-azotoluene, accelerates the development of liver tumors.

If biomycin is administered to an animal it is concentrated in the liver [2]. It leaves the liver with the bile for the intestine, where it is partly absorbed, and reenters the liver. Because of the long stay of the antibiotic in this organ, it may possess an unfavorable effect on hepatic function.

In the investigation described below the action of biomycin was studied on induced carcinogenesis in the liver.

EXPERIMENTAL METHOD

Altogether 405 male hybrid CBA × C57BL mice weighing 18-20 g (at the beginning of the experiment) were used. The compound chosen as heptatotropic carcinogen was o-aminoazotoluene (OAAT) in 1% solution in benzene, and it was applied to a preliminary shaved area of skin in the interscapular region of the mice three times a week for 11 months (total 130 applications).

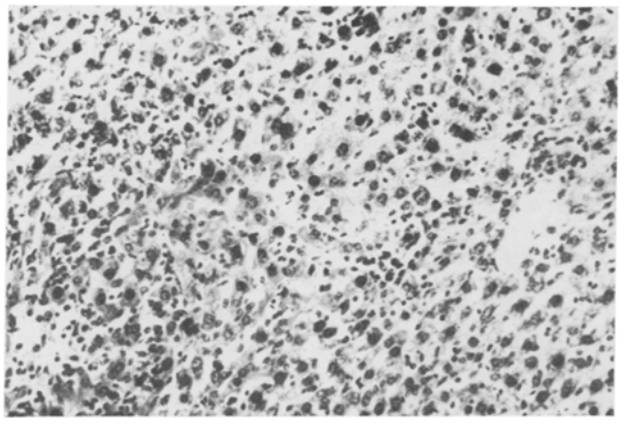

Fig. 1

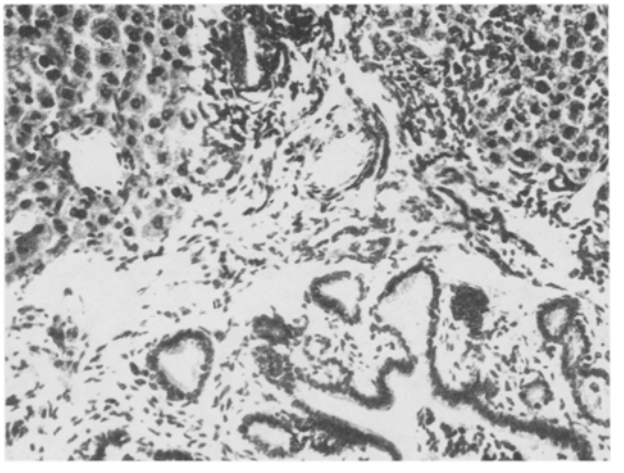

Fig. 2

Fig. 1. Hepatocellular carcinoma. Hematoxylin-eosin, 200×.

Fig. 2. Carcinoma of bile ducts. Hematoxylin-eosin, 200×.

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TABLE 1. Effect of Biomycin on Carcinogenesis Induced by OAAT in the Liver

Group of mice	Characteristics of group	No. of animals at beg. of expt.	No. of animals with tumors by months (in percent)									
			1	2	3	4	5	6	7	8	9	10
1	Injection of biomycin before beginning of OAAT applications	114	0	0	0	12,5	15 $P>0,5$	24 $P>0,2$	28	24 $P>0,5$	30 $P>0,5$	35 $P>0,5$
2	Injection of biomycin during first week of experiment	73	0	20	33	37	30 $P>0,2$	33	29	28	35	35
3	Injection of biomycin in 6th week of experiment	75	0	17	12,5	17	37,5 $P>0,2$	35	37,5 $P>0,2$	33,5 $P>0,5$	48 $P>0,2$	49 $P>0,2$
4	Injection of biomycin in 26th week of experiment	65	0	0	0	0	0	0	0	11 $P>0,2$	38	47 $P>0,2$
5	Control	78	0	0	0	0	20	33	28,5	27,5	35	37,5

Biomycin, dissolved in distilled water, was injected subcutaneously into the mice in a dose of 15 mg/kg once daily for 7 successive days at different stages of carcinogenesis induced by OAAT.

The animals of group 1 received the antibiotic before applications of OAAT began. The first application of the carcinogen was given on the day of the last injection of antibiotic. Mice of the second group began to receive biomycin at the same time as the first application of carcinogen and continued to receive it daily for the first week of the experiment. The animals of group 3 received biomycin on the 6th week of the experiment, and those of group 4 on the 26th week. The mice of group 5 (control) did not receive injections of biomycin.

EXPERIMENTAL RESULTS

The experimental results are given in Table 1. In animals receiving biomycin before the beginning of applications of the carcinogen and during the first week thereafter showed considerable acceleration of the formation of liver tumors compared with the control, by one and three months respectively. In the group of animals receiving biomycin in the 6th week of the experiment, the first tumor likewise was found three months sooner than in the controls. The results in this table also show a marked increase in the percentage of animals with tumors (by 33 and 37) in group 2 compared with the control at the 3rd and 4th months, while in group 3, receiving biomycin in the 6th week of the experiment, the number of animals with tumors only showed a tendency to increase. At later stages a gradual increase in the number of animals with tumors was observed in both the experimental and control groups. By the end of the experiment the number of animals with liver tumors in the experimental groups was not significantly different from the number in the control.

In mice sacrificed before discovery of the first liver tumors, slight enlargement of the liver was found one month after the beginning of OAAT applications on macroscopic examination; subsequently small, solitary or multiple nodules as large as millet seeds, and of various colors, appeared in it. Gradually the visible changes in the liver increased, and sometimes the organ was considerably enlarged and its entire surface became granular. Less frequently, large nodules appeared, and microscopic examination showed them to be malignant tumors.

Microscopically, one month after the beginning of the experiment, marked changes in the liver tissue were observed, consisting of some increase in the size of the individual cells and the presence of mitotic figures in larger numbers than in the normal liver. A little later, some atypical liver cells were observed: these were unequal in size, numerous binuclear or even polynuclear cells appeared, and in some cases giant cells were observed. The cell cytoplasm became reticular in structure and contained

a few vacuoles. Diffuse hyperplasia and hypertrophy of the liver cells occurred, leading to disturbance of the general structure of the liver. Nearly all the tumors were identical in structure. They were classed as hepatocellular carcinoma (Fig. 1). The tumor nodules consisted either of an irregular accumulation of polymorphic, atypical cells, growing by infiltration, or of liver cells of uniform size forming tubules. The liver cells differed sharply from normal. They varied considerably in size from small to giant. The cytoplasm was highly vacuolated. The nuclei were greatly enlarged and their shape highly abnormal.

At the same time, in very rare cases tumors consisting of bile duct cells were observed, the liver cells containing retained bile in the form of brown granules (Fig. 2). Hence, this investigation revealed the development of many liver tumors, mostly hepatocellular carcinomas, and in animals receiving biomycin in the early stages of the process, tumor formation occurred much more rapidly than in the control. The reason must be a disturbance of tissue metabolism. It has been reported in the literature that antibiotics of the tetracycline group, especially biomycin, have a direct stimulant effect on metabolism in animals [3]. Findings have also been obtained showing that chlortetracycline influences the synthesis of protein and nucleic acids, and also has an effect on enzyme activity [1, 4].

Investigations have also shown that besides biomycin, a culture of Streptomyces aureofaciens also secretes certain growth-stimulating factors, notably vitamin B_{12} [2]. The effect of biomycin in stimulating carcinogenesis in the present experiments may perhaps be associated, therefore, with the influence of this vitamin.

LITERATURE CITED

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