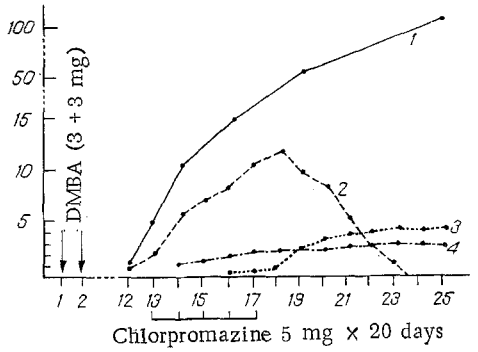

Fig. 1. Development of mammary gland carcinoma induced by DMBA in female rats with different hormonal status. Abscissa, time of observation (in weeks); ordinate, volume of tumor (in cm^3); 1) division of pituitary stalk; 2) chlorpromazine; 3) control; 4) division of pituitary stalk + ovariectomy.

blood prolactin and estrogen concentrations can be chosen as criteria for the identification of groups of women with a high risk of development of hormone-dependent mammary gland tumors and for the choice of methods of their treatment. To break this pathological hormonal chain (prolactin + estrogens) and, in particular, for the treatment of mastopathies, substances suppressing prolactin secretion (ergot alkaloids and, in particular, parlodel, L-dopa, etc.) must be combined with antiestrogens.

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EFFECT OF MISCLERON (CLOFIBRATE) ON INDUCTION OF INTESTINAL TUMORS BY DIMETHYLHYDRAZINE IN RATS

L. M. Bershtein, K. M. Pozharisskii, and V. M. Dil'man

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KEY WORDS: rats; intestinal tumors; dimethylhydrazine; Miscleron (clofibrate).

In harmony with views on the role of disturbances of lipid and carbohydrate metabolism in the creation of conditions promoting tumor growth [1, 2], the hypolipidemic drug Miscleron (clofibrate) has been used for several years for the correction of these disturbances in cancer patients suffering, in particular, from carcinoma of the colon and rectum [3]. Besides these considerations, support for the validity of this therapeutic approach has recently been obtained from a steady flow of information on cholesterol and certain of its derivatives and the bile acids as promotors of carcinogenesis in the large intestine [5, 8]. However, the use of hypolipidemic agents such as cholestyramine and candicidin in experiments on rats not only did not inhibit the development of tumors of the large intestine under the influence of azoxymethane, but actually potentiated this process [15]. Meanwhile, in an international investigation conducted over the last few years by Professor Oliver, to study primary prevention of ischemic heart disease by clofibrate, it was shown that the number of myocardial infarcts not ending fatally was significantly reduced in the group of subjects taking the drug, and on standardization of the data for age, the number of malignant neoplasms developing (including those in the gastrointestinal tract) did not differ significantly from the control values, i.e., in subjects receiving a placebo [7].

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TABLE 1. Effect of Clofibrate on Number and Size of Intestinal Tumors Induced by DMH and on Blood Lipid Level in Rats (M ± m)

Group of animals	Experimental conditions	Number of rats	Number of tumors per rat			Mean volume of tumors, mm³ (number of tumor nodules in parentheses)			Blood lipid concentration, mg% (number of determinations in parentheses)		
			intestine	made up of		intestine	made up of		cholesterol	total lipoproteins	triglycerides
				large intestine	small intestine		large intestine	small intestine			
1	DMH + clofibrate for 10 days before DMH	16	9,3±1,8	9,0±1,9	0,31±0,1	80±25 (152)	66±10 (147)	498±318 (5)	55,3±3,1 (13)	316±18 (13)	64±16 (13)
2	DMH + clofibrate simultaneously	17	6,3±1,0	5,8±1,1	0,53±0,1	162±43 (106)	134±58 (97)	466±117 (9)	58,2±3,4 (17)	360±21 (17)	71±10 (17)
1—2	DMH + clofibrate (combined data)	33	7,8±0,9	7,4±1,0	0,42±0,1	114±31 (258)	93±32 (244)	471±130 (14)	56,8±1,9 (30)	341±13 (30)	68±8 (30)
3	DMH (control)	13	8,8±1,3	8,5±1,4	0,30±0,1	403±322 (115)	386±166 (111)	859±322 (4)	58,5±2,9 (12)	347±40 (12)	107±20 (12)

Considering the importance of the results of the investigation by Oliver et al. [9, 10], and also differences in the mechanism of action of clofibrate, cholestyramine, and candicidin [12, 15], it was decided to study the effect of clofibrate on carcinogenesis induced by dimethylhydrazine (DMH) in the intestine in rats.

EXPERIMENTAL METHOD

Experiments were carried out on three groups of male rats (from "Rappolovo" Nursery), with a body weight of 200 to 220 g at the beginning of the experiment. For 20 weeks all the animals received DMH·2HCl subcutaneously in a dose of 14 mg/kg body weight, calculated as the base, once a week. Clofibrate was given in a dose of 25 mg daily *per os*, corresposing to approximately 120 mg/kg body weight at the beginning of the experiment and 70 mg/kg body weight at its end, five times a week to the rats of group 1 10 days before the first injection of DMH and to the rats of group 2 from the moment of the first injection of DMH and until the end of the experiment. The rats of the third group received 1-1.5 ml water *per os* through a tube under the same conditions. The animals were kept on an ordinary diet and were weighed weekly. No significant differences were found in the dynamics of the body weight in the course of the experiment in the rats of the various groups compared. The animals were decapitated 25 weeks after the first injection of DMH, after preliminary starvation for 14-16 h; the number of neoplasms in the large and small intestines was counted and their dimensions measured in three mutually perpendicular directions (the product obtained by multiplying these three measurements was used to represent the conventional volume of the tumor). Tumors of the large and small intestines, after appropriate histological treatment, were examined microscopically to confirm the diagnosis. The levels of cholesterol [14] and of total lipoproteins [4] and triglycerides [6] were determined in blood obtained during decapitation. The numerical results were subjected to statistical analysis by Student's method.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that clofibrate had virtually no effect on the frequency of tumors arising in the large and small intestines of the rats. Meanwhile a tendency was

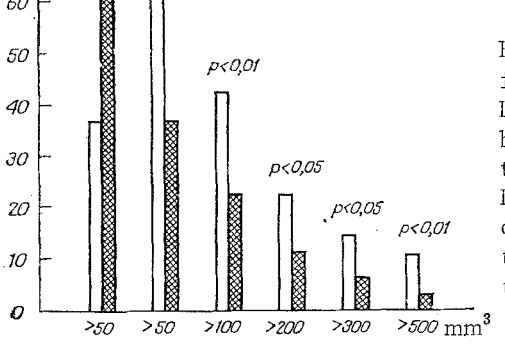

Fig. 1. Distribution of tumors of large intestine by volume in rats receiving DMH (unshaded columns) and DMH + clofibrate (shaded columns). Numbers of tumors investigated in rats receiving DMH 111; number in rats receiving DMH + clofibrate 244. Abscissa, volume of tumor (in mm³); ordinate, number of tumors (in %).

observed for the mean volume of the tumor nodules to be reduced in rats receiving clofibrate, especially as regards neoplasms of the large intestine in the animals of group 1. There was also a tendency for the blood triglyceride level to be lower in animals receiving clofibrate. The decrease in volume of the tumor nodules in the rats of groups 1 and 2, which received clofibrate, took place on account of a significant decrease (compared with the control animals) in the number of neoplasms with a volume of over 50 mm^3 (Fig. 1).

Consequently, although it did not affect the frequency of appearance of tumor nodules in the intestine, clofibrate inhibited the further growth of these tumors. The information on the use of clofibrate in experimental oncology is limited in amount, and the aim of the investigations was not always to study the antitumor activity of the drug [13, 17, 19]. More recently, besides the discussion of this problem in connection with the publication of the paper by Oliver et al. [7], the interest of research workers has been drawn to a communication by Gold [11], who showed that clofibrate can potentiate the inhibitory action of hydrazine sulfate and of various cytostatics on growth of Walker's carcinosarcoma. As regards the mechanisms of the effect of clofibrate found in the present investigation, the following main possibilities must be considered: 1) weakening of the intensified metabolism and excretion of cholesterol and bile acids with the feces induced by DMH [16]; 2) inhibition of cholesterol synthesis actually in the intestinal wall [12]; 3) a fall in the blood lipid level and abolition of the metabolic component of the cancrophilia syndrome [1-3]; 4) action through the immunologic system, based on abolition of metabolic immunodepression [2] and on stimulation of certain other immunologic reactions [18]; 5) inhibition of gluconeogenesis [11], and so on. However, whatever the mechanism of the phenomenon discovered, the results obtained in the present investigation are further experimental confirmation of the value of the use of clofibrate and related preparations in oncology.

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