The duration of the S and G_2 periods of MC in mono- and binuclear hepatocytes of normal animals thus varies in the course of the 24-h period. Unlike fluctuations in the duration of the G_2 period, which occur at the same time of day in the two cell populations, the rhythmic fluctuations in ts in these two populations are not synchronized. Under the influence of throxine the duration of the G_2 period is reduced in mono- and binuclear hepatocytes, but the decrease differs at different times of day. The effect of throxine on the duration of the S period in the two populations differs depending on the clock time and may be expressed either as a decrease or as an increase in ts. Treatment with throxine leads to more synchronized variations in tS during the 24-h period in mono- and binuclear hepatocytes. Incidentally throxine does not cause changes in the mean diurnal duration of the S period compared with that observed in normal animals.

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HUMAN INTERFERON-INDUCED INHIBITION OF MOUSE LIVER REGENERATION

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Proteins of the interferon family are active regulators of cell proliferation both in the intact organism and in cell culture [7]. The antiproliferative activity of interferon, combined with its activation of certain components of cell-mediated immunity, evidently constitutes the basis for the recently widely studied antitumor effect of this protein. Several aspects of the antiproliferative action of interferon can be analyzed in a purer form by studying its effect *in vivo* on regeneration.

Gresser et al. [4, 5] reported a decrease in the number of thymidine-^{3}H-labeled cells in the regenerating liver 48 h after partial hepatectomy, following injection of homologous fibroblast interferon.

The aim of the present investigation was to study the effect of both homologous (mouse) and heterologous (human) interferons on restoration of the weight of the regenerating mouse liver and also on proliferative activity of hepatocytes and Kupffer cells.

EXPERIMENTAL METHOD

Experiments were carried out on 75 noninbred mice weighing 20-26 g. Two-thirds of the liver was removed in 45 animals by the usual method [6]. Immediately after the operation and daily for the next 3 days the animals were given an intramuscular injection of 0.2 ml of partially purified and concentrated mouse fibroblast interferon (M-IFN) (group 1) [1], in a dose of $5 \cdot 10^3$ units/mouse, human leukocytic interferon (4-IFN), purified by the method in [3], in a dose of $0.5 \cdot 10^5$ unit/mouse (group 2), or a preparation of pseudointerferon from human cells (group 3). The same preparations were injected at the same intervals into control animals not subjected to hepatectomy.

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TABLE 1. Changes in Weight of Liver and Spleen in Partially Hepatectomized and Intact Mice under the Influence of Interferon and Its Analog

Group of animals	Preparation injected	Weight of mice at end of experiment, g	Weight of liver		Weight of spleen	
			% of body weight	% of control	% of body weight	% of control
Control	M-IFN	23,6	7,0±0,22		0,73±0,07	
Experiment (group 1)		22,2	5,3±0,12	76	0,84±0,13	115
Control	4-IFN	22,0	6,8±0,20		0,51±0,07	
Experiment (group 2)		20,7	4,4±0,30	65*	0,58±0,09	113
Control	Pseudointer-feron	23,0	6,7±0,3		0,50±0,03	
Experiment (group 3)		20,5	5,5±0,5	82	0,65±0,06	130†

*Differences compared with group 3 and with group 1 significant.
†Differences between group 3 and control significant.

TABLE 2. Changes in Mitotic Index (MI) of Hepatocytes and Kupffer Cells in Liver of Partially Hepatectomized and Intact Mice under the Influence of Interferon and Its Analog

Group of animals	Preparation injected	Number of mice	Cells	MI ‰	
				control	experiment
1	M-IFN	15	Hepatocytes	0	0,40*±0,06
			Kupffer cells	0,51*±0,11	1,51±0,25
2	4-IFN	14	Hepatocytes	0,03±0,02	0,28*±0,07
			Kupffer cells	0,48*±0,23	2,29±0,48
3	Pseudointerferon	9	Hepatocytes	0	0,75±0,14
			Kupffer cells	1,10±0,16	2,28±0,48

*Differences compared with group 3 significant.

All the animals were killed 24 h after the last injection (i.e., 4 days after the operation). The liver was weighed, fixed in Carnoy's fluid, and paraffin sections 4-5 μ thick were stained with hematoxylin and eosin.

The completeness of restoration of the mass of the regenerating liver was determined by calculating the ratio between the weight of the liver in the experimental animals and its weight in the control mice. These ratios were expressed as percentages.

Mitotic activity of the cells was expressed in promille after counting the number of mitoses in 6000-8500 hepatocytes and in 3000-5500 Kupffer cells (MBB-1 microscope, magnification 630). The numerical results were subjected to statistical analysis by the Fisher–Student method.

EXPERIMENTAL RESULTS

Animals receiving M-IFN or 4-IFN were more resistant to the operation than mice receiving its analog (pseudointerferon). Their postoperative mortality was only half as high. Meanwhile restoration of the weight of the liver was less complete under the influence of interferon than after injections of pseudointerferon. This was particularly clear when purified human interferon was used. As Table 1 shows, by the 4th day the weight of the liver in the mice of group 3 (pseudointerferon) was restored up to 82% of the control level. In the mice of group 2 (4-IFN) the degree of recovery of weight of the liver was significantly lower (65%) than in the animals of groups 1 and 3 ($P = 0.013$ and 0.0001).

In the animals not undergoing hepatectomy the weight of the liver was unchanged by administration of the various preparations.

It will be noted that M-IFN increased the weight of the spleen by 46% in mice not undergoing hepatectomy, whereas 4-IFN had no such action. Operations on the liver usually cause enlargement of the spleen [2]. After administration of pseudointerferon, this process was manifested clearly. Both interferon preparations abolished this enlargement of the spleen in the partially hepatectomized mice (Table 1).

The results of analysis of proliferative activity of the hepatocytes and Kupffer cells (Table 2) show that both interferons, irrespective of species, exhibited an antiproliferative

action, reducing mitotic division abruptly in the hepatocytes of the regenerating liver and in the Kupffer cells of the intact mice. The proliferative activity of the Kupffer cells in the partially hepatectomized animals of all three groups was approximately equal and was significantly higher than the control level.

On the whole these results are evidence that, irrespective of the species of origin of the interferon, it led to a persistent decrease in the proliferative activity of the regenerating liver cells. The persistence of this effect is shown by the retarded gain in weight of the liver in the experimental animals, which was particularly clearly marked in mice receiving the highly purified human interferon.

The discovery of inhibition of regeneration of the liver in mice by preparations of human interferon may provide a convenient model with which to study the antiproliferative activity of such preparations *in vivo*.

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POTENTIATING THE ABILITY OF MOUSE LYMPHOCYTES TO TRANSFER "REGENERATION INFORMATION" BY REPEATED LIVER RESECTION

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Lymphocytes of partially hepatectomized (resection of $^2/_3$ of the liver) and of unilaterally nephrectomized mice are known to have the property of potentiating proliferation and growth of the corresponding organs in intact syngeneic animals [1, 2, 5, 7, 8]. This phenomenon can conventionally be called the transmission of "regeneration information."

The object of the present investigation was to study the ability of lymphocytes to transfer "regeneration information" during repeated operations on the liver, and depending on the quantity of tissue removed.

EXPERIMENTAL METHOD

Three practically identical series of experiments (four groups of experiments in each series) were carried out on 250 sexually mature male CBA mice. The general scheme of the experiments was as follows. An injection of $7 \cdot 10^7$ lymphocytes, isolated from the spleen by the method used previously [1, 3], in medium 199 was given into the caudal vein of intact mice. The donors of the lymphocytes for recipients of group 1 were mice from which two lobes of the liver had been removed by the usual method in one stage [6].

The donors for the recipients of group 2 were mice from which these lobes had been resected in two stages. The second operation was performed 20 days after the first, which corresponded to a period of 2 weeks after restoration of the weight of the liver.

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