It thus follows from these experiments that mature infectious viruses are synthesized in cells of an unnatural host (man), transformed by heterologous viruses (lines 23 and P-2). However, compared with the original strains of Rous and polyoma virus, the properties of these viruses were changed: They showed increased affinity for mammalian tissues and changes in the protein membranes of the viruses. It is interesting to note that polyoma virus caused both productive (synthesis and liberation of virus particles) and integrative (conversion of cells from normal to malignant) forms of infection when acting on human embryonic cells.

In recent years several workers have shown that the infectivity of an oncovirus depends on the degree of homology of its genome with the nucleic acid of the host cell and also that genetic recombination of the oncovirus with the cell DNA is possible [10]. Accordingly it can be suggested that the genomes of Rous and polyoma viruses, as a result of prolonged replication in cells of the new host (man), have incorporated part of his genetic material, thus leading to their greater homology with the new host, as a result of which their affinity for human cells was increased and their protein membrane modified.

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ROLE OF THE LIVER IN DEVELOPMENT OF DYSHORMONAL DISEASES OF THE MAMMARY GLAND IN RATS

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Intermittent administration of CCl_4 combined with permanent illumination led to a decrease in the frequency of mastopathy and mammary gland tumors in sexually immature female rats and lengthened the period of their development. It is suggested that during regression of cirrhosis the liver may lose its ability to activate estrogens.

KEY WORDS: estrogens; cirrhosis of the liver; mastopathy.

According to data in the literature, prolonged and intermittent administration of CCl_4 to mice and rats causes cirrhosis of the liver, which is accompanied by hyperestrogenization of the animal, leading to the subsequent development of mastopathy and tumors of the mammary gland [1, 2, 4, 8]. It has also been shown that after exposure to CCl_4 ends, the structure and function of the damaged liver are restored [3, 7, 9].

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TABLE 1. Dyshormonal Diseases of Mammary Gland in Rats Treated with CCl_4

Experiment number	Age at beginning of exposure	Group	Number of rats	Follicular cysts of ovaries		Mastopathy		Mammary gland tumors		Minimal latent period, months		
				absolute	%	absolute	%	absolute	%	follicular cysts	mastopathy	mammary gland tumors
1	3.5-4 months											
		Control	19	11	58	5	26	1	5	7	7	9,5
		CCl_4	18	9	50	5	28	1	5	8	10	13
2	12 months											
		Control	31	16	52	23	74	5	16	2	2	2
		CCl_4	43	17	40	16	37	7	16	2	2	2
						$P<0,01$						
3	3-4 weeks											
		Control	100	17	17	0	—	1	1	6,5	—	11,5
		Illumination	83	67	81	61	74	9	11	1,5	6	9
		Illumination + CCl_4	88	2	2	3	3	1	1	9	12	13
				$P<0,001$		$P<0,01$		$P<0,001$				
4	10-12 months with permanent estrus											
		Control	23	21	91	21	91	5	22	—	2	2
		CCl_4	29	16	55	12	41	6	21	—	2	2
				$P<0,05$		$P<0,001$						

The object of this investigation was to study the effect of temporary intermittent administration of CCl_4 on the development of dyshormonal diseases of the mammary gland in rats, in the presence or absence of follicular cysts in their ovaries.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred female rats of different ages in four series. In series 1 rats were aged 3.5-4 months, and in series 2 they were aged 12 months. In series 3 the development of follicular cysts of the ovaries was induced in sexually immature rats by permanent illumination [6]. In series 4 rats aged 10-12 months with spontaneous permanent estrus were selected. One group of rats from each series was given CCl_4, which was injected subcutaneously twice a week in a dose of 0.01 ml/100 g body weight, as a 40% oily solution for 6 months, with two interruptions 3 and 8 weeks, respectively, after the beginning of the experiment, lasting 3 and 2 weeks. Altogether 44 injections were given. The longest period of observation was 13 months in series 1 and 3 and 9 months in series 2 and 4, after which all the rats which were still alive were killed. The ovaries, uterus, mammary glands, and liver of the dying and killed animals were treated histologically in the usual way.

EXPERIMENTAL RESULTS

The results are given in Table 1. They show that in the rats of series 1, after administration of CCl_4 the development of follicular cysts of the ovaries, mastopathy, and tumors of the mammary gland (fibroadenomas) was observed with the same frequency as in the control animals; however, the CCl_4 increased the minimal latent period of development of mastopathy from 7 to 10 months, and of tumors from 9.5 to 13 months.

In the rats of the second series, which began to receive CCl_4 at the age of 12 months, a marked decrease was observed in the frequency of mastopathy (37% in the experimental animals compared with 74% in the control); the frequency of development of mammary gland tumors (fibroadenomas and carcinoma), and also of follicular cysts of the ovaries, however, was practically unchanged. Pathological changes in the mammary gland and ovaries were first observed two months after the beginning of observation in both the experimental and control groups.

During exposure to CCl_4 in series 3 a sharp decrease was observed in the frequency of follicular cysts of the ovaries (2% during administration of CCl_4 and 81% during illumination alone) and the frequency of development of pathological changes in the mammary gland fell considerably. After illumination mastopathy was found in 74% of rats, but after additional treatment with CCl_4, in only 3%. Mammary gland tumors were present in 11 and 1% of rats, respectively. In the control group of rats mastopathy could not be detected in a single animal, and fibroadenoma was present in only 1 of 100 rats. The minimal latent period of development of the

follicular cysts in this series of experiments increased from 1.5 months in animals exposed to illumination only to 9 months in rats receiving CCl_4 in addition. The latent period of development of mastopathy and of tumors also was increased from 6 to 12 and from 9 to 13 months, respectively.

In the rats of series 4 injection of CCl_4 reduced the frequency of follicular cysts of the ovaries (from 91% in the control to 55% in the experimental rats) and of mastopathy (from 91 to 41%), but the frequency of tumor development was unchanged (22 and 21%). Pathological changes in the mammary gland of the rats of both groups were first found after two months.

By contrast with the results obtained previously on induction of mastopathy and mammary gland tumors in rats during prolonged and interrupted administration of CCl_4, in the present experiments temporary interrupted exposure to the hepatotoxic poison caused a marked decrease in frequency and an increase in the latent period of development of follicular cysts of the ovaries and dyshormonal diseases of the mammary gland. The most marked proliferative action was observed in the case of permanent illumination of rats sexually mature when chosen for the experiment. In old animals, just as in rats with spontaneous permanent estrus, frequency of development of mammary gland tumors after treatment with CCl_4 was unchanged.

Histological examination of the liver showed that treatment with CCl_4 as a rule caused the development of cirrhosis, but toward the end of the experiment, after cessation of CCl_4 administration, clear signs of regression of the cirrhosis and restoration of the structure of the organs were observed in many rats.

There are three possible explanations of the prophylactic action of CCl_4 in this investigation. First, activation of estrogens produced by the ovaries may be depressed in the damaged liver [5]. Second, during regression of cirrhosis the liver may recover its function of inactivation of estrogens, as other workers have already observed [10]. This second suggestion was confirmed by the absence of hyperplastic changes in the uterus, which is most sensitive to elevation of the estrogen level in the body, in rats with signs of recovery of the structure of the liver. Finally, the prophylactic effect may be connected with the direct harmful action of CCl_4 on the ovaries and the consequent change in the function of the hypothalamic–hypophyseal system. For instance, in many rats in series 4, which had follicular cysts in their ovaries, corpora lutea appeared after exposure to CCl_4, i.e., normalization of their ovarian function took place. In most animals of the second and third series, treated with CCl_4, the histological structure of the ovaries was normal. The decrease in the frequency of mastopathy in the rats of these groups could evidently be attributed to this fact.

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