high dose rates would lead to toxic concentrations of the same or other substances.

Summary. Beta radiation administered at a level of from 0.77 to 3.13 rep per hour and X-ray radiation given at 4 or 8 r per hour stimulates reproduction in paramecium. The stimulation is not due to mutation since it disappears immediately on removal of the cell from the influence of the radiation.

Received May 21, 1953. P.S.E.B.M., 1953, v83.

Effect of Intravenous Administration of Paritol-C* on Serum Lipids of Hypercholesterolemic Rabbits.† (20451)

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Previous work in our laboratory showed that only a relatively small percentage of the cholesterol of lyophilized normal human or rabbit serum can be extracted by cold chloroform even in 24 hours, while a large percentage of the serum cholesterol of nephrotic patients and hypercholesterolemic rabbits can be thus extracted(1). The fraction extractable in a 3-hour period, which is usually practically the same as extracted in 24 hours, has been called the "readily extractable" cholesterol.

Gofman and associates(2,3) have shown that heparin administration causes a shift in the lipoproteins of high Sf values into those of successively lower ones in the serum of hypercholesterolemic rabbits and human subjects. Nikkilä(4) obtained the same general effect. Injection of heparin also has been shown to suppress the rate of development of atherosclerosis in cholesterol fed rabbits(3). Since the anticoagulant Paritol exerts the same general effect as heparin on blood coagulation and has been shown to affect serum lipoproteins (5), it was decided to determine if its administration would favorably influence the concentration of the "readily extractable" fraction and that of total cholesterol in hypercholesterolemic rabbits.

Experimental. Male rabbits, weighing between 4 and 5 lb except when otherwise stated, were put on a 0.5% cholesterol diet prepared as follows. Fifty g of cholesterol were dissolved in 100 ml of chloroform and added to 500 g of Wesson oil. After warming on a water bath until practically all of the cholesterol was again in solution, the whole was added to 9450 g of Rockland rabbit pellets and thoroughly mixed. The diet was ready for feeding after all the chloroform had evaporated. It was fed to all the animals throughout the whole experimental period. The Paritol was injected intravenously using a 5% solution. Blood for the analytical studies was obtained by nicking an ear vein after the ear had been warmed with a heat lamp. The analytical procedures employed have been described previously(1).

In Exp. 1, after the animals were on the high cholesterol diet for about 12 weeks, the Paritol injections were begun. The total cholesterol by this time had reached an average of 1750 mg/100 ml of serum and the "readily extractable" fraction constituted 90% of the whole. The Paritol injections were given in amounts corresponding to 0.1 ml of a 5% solution/lb body weight. It will be seen from the results, which have been averaged in Table I, that the Paritol injections caused a marked drop in all the fractions studied. This was true in each individual animal as well as in the average for the group. The percentage of the total cholesterol present in the "readily extractable" form tended to decrease as the total cholesterol decreased. This was very marked in all individual cases where the total cholesterol had dropped to

* A polysulfuric acid ester of polyanhydromanuronic acid kindly supplied by Wyeth, Inc., Philadelphia.

† Presented at the annual meeting of the Virginia Academy of Science, May, 1953.

TABLE I. Effect of Intravenous Administration of Paritol-C on Serum Lipids of Hypercholesterolemic Rabbits.

Exp. No.	No. of animals	Avg conc. of serum lipids: T. chol.	R.E. chol.	N.F.+ chol.	R.E. chol. as % T. chol.	Serum collection, total elapsed time, days	Remarks
		%	%	%			High cholesterol diet 12 wk
1	8*	1.75	1.57	2.61	90	0	Control sera before Paritol
		1.09	.80	1.58	73	3	Same animals, Paritol 2 days. Bled 24 hr after last inj.
		.76	.54	1.36	71	6	Same animals, Paritol 2 additional inj. Bled 24 hr after last inj.
							High cholesterol diet 3 wk
2	4*	1.46	1.30	2.65	90	0	Control sera before Paritol
		.87	.58	1.31	67	14	Same animals, Paritol 2 inj. a wk for 2 wk. Bled 72 hr after last inj.
		.76	.64	1.31	84	28	Same after 3 inj. a wk for 2 more wk. Bled 48 hr after last inj.
		.74	.54	1.17	73	42	Same after similar inj. for 2 more wk. Bled 48 hr after last inj.
	3	.90	.75	1.32	83	0	Pair-fed controls. No Paritol
		1.31	1.08	2.00	82	14	Animals bled at same time as corresponding Paritol inj. animals
		1.76	1.67	2.88	95	28	
		2.69	2.48	4.33	92	42	
							High cholesterol diet 6 wk
3	3*	2.29	2.13	3.46	93	0	Control sera before Paritol
		1.18	1.14	2.00	97	5	Same animals, Paritol 2 days. Bled 72 hr after last inj.
		1.25	1.13	2.00	90	9	Same after 2 inj. alternate days. Bled 48 hr after last inj.
		.87	.62	1.30	71	14	Same after 2 more inj. alternate days. Bled 72 hr after last inj.
		.68	.31	1.10	45	21	Same after 3 more inj. alternate days, then 2 inj. consecutive days. Bled 24 hr after last inj.
		.69	.30	1.05	43	26	Same after 4 more inj. consecutive days. Bled 48 hr after last inj.
	2	2.27	2.12	3.39	93	0	Pair-fed controls. No Paritol.
		1.82	1.83	3.52	100	5	Animals bled at same time as corresponding Paritol inj. animals
		1.54	1.36	2.24	88	9	
		1.68	1.63	2.44	97	14	
		1.57	1.43	2.35	91	21	
		1.40	1.17	2.02	83	26	

* Blood samples from Paritol-injected animals were obtained just before next injection.
T. chol. = Total cholesterol. R.E. chol. = Readily extractable cholesterol. N.F. + chol. = Neutral fat plus cholesterol.

around 700 mg %. Actually no test animal in any experiment with a total cholesterol below 600 mg % showed over 40% of the total cholesterol present in the "readily extractable" form.

In Exp. 2 the animals were on the high cholesterol diet for only 3 weeks when the Paritol injections were begun. Four of the animals were given Paritol and 3 were kept as controls so as to show the effect of the diet alone on the lipid fractions under study. Each injected animal received 1 ml of the 5% Paritol solution at each injection. All animals were fed throughout the whole experimental period, except for the first couple of days, 20 g of diet/lb of body weight as deter-

mined at the time of the first Paritol injection. The injected animals ate very poorly for 2 days following the first Paritol injection, so the food intake of the controls was kept down to 10 g/lb of body weight during this period. Subsequent injections of the anticoagulant did not affect the animals' appetites in any way and all ate the full 20 g/lb of body weight, except on several occasions when a small amount was left, especially by the controls. It will be seen that the Paritol injections caused a drop of around 50% in the concentration of the various lipid fractions, while at the same time the concentrations of these fractions in the sera of the control animals rose to a high level during the same period. In the control series (Table I, Exp. 2) 2 of the animals were fairly resistant to the development of hypercholesterolemia as indicated by a considerably lower total cholesterol level at the time the Paritol injections were begun, but developed high values as the experiment progressed. All animals gained between 1.25 and 1.5 lb in weight during the experimental period. The animals used in Exp. 3 were in the laboratory for several months before they were used and were considerably larger than those used in the other experiments. Their general appetite was considerably less than that of the animals used in Exp. 2. They were on the cholesterol diet for 6 weeks before the injections were begun and by this time the average total cholesterol was 2280 mg % of which the "readily extractable" fraction constituted over 90%. Since the animals were not eating well, only 10 g of food/lb body weight was fed each day. The test animals always ate their food but one control often left some. This animal, however, in spite of its lower food consumption, consistently exhibited a higher serum cholesterol concentration than its accompanying control. The same general results were obtained in this experiment as in the previous ones. In this experiment, however, even the control animals showed a decided drop in the various fractions, but it was small compared with that of the injected animals. The difference in the response of the controls in this experiment and in Exp. 2 is undoubtedly due to the fact that their food consumption, and consequently cholesterol intake/lb of body weight was only about 50% of that of the animals in Exp. 2.

When the data are examined as a whole, it will be seen that the changes in the neutral fat plus cholesterol tended to follow rather closely those of total cholesterol, a decrease or increase in one being usually accompanied by a roughly proportional change in the other. Since the neutral fat plus cholesterol fraction includes free cholesterol, ester cholesterol, and neutral fat the changes noted in this fraction are additional evidence in support of the observed changes in total cholesterol following the Paritol injections.

Phospholipid phosphorus determinations were carried out on all sera and they were found to vary more or less with the total cholesterol. The anticoagulant Dicumarol was injected intravenously at a level of 50 mg/day for 2 days into several animals without any effect on any of the lipid fractions being studied.

Summary. The intravenous injection of Paritol-C into hypercholesterolemic rabbits has been shown to cause a marked drop in the "readily extractable" cholesterol fraction, as well as in total cholesterol.

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Received June 1, 1953. P.S.E.B.M., 1953, v83.