

the basis of potentially free penicillin, Cavillito *et al.*² reported that the benzyl ester was more active than pure penicillin in the treatment of experimental streptococcal infections in mice. However, the benzyl ester was administered in sesame oil. Since this preparation is oil soluble and water insoluble, it is likely a more prolonged plasma level of free penicillin was obtained with the benzyl ester as compared to the sodium salt. The apparent increased activity of the benzyl ester in their experiments was therefore probably due to delayed absorption, rather than to any inherent increase in activity of the benzyl ester. The evidence available at the present time

indicates that it would be hazardous to transfer results obtained in mice to man. Whether man can hydrolyze either of these esters to a significant degree can only be determined by further study.

Conclusions. Plasma levels following administration of benzyl and methyl esters of penicillin G have been determined in a variety of species of animals. Mice hydrolyze both of these esters rapidly and probably completely. Rats are able to hydrolyze the esters less completely. Monkeys, dogs, and rabbits show no appreciable plasma level of free penicillin following subcutaneous injection of ordinary doses of these esters.

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"Renal Hyperlipemia" in Dogs and Rats.*

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Previous work¹ has shown that unilateral and bilateral nephrectomy and also the administration of nephrotoxic agents like mercury bichloride, uranium nitrate, and potassium dichromate regularly increase blood lipid concentration in dogs. Hyperlipemia of the same pattern occurred, however, once after 4 sham operations, three times after 5 splenectomies, and was regularly observed after severe tissue necrosis. It was concluded that the kidneys of dogs, cats, rats, and monkeys are part of a mechanism which influences blood lipid concentration. These studies prompted further investigations to separate more clearly the influence of extrarenal tissue injury from the effect which renal tissue exerts on blood lipid concentration.

Methods and operative procedures have been described previously.¹ In order to eliminate the complicating factor of a general anesthesia, *unilateral nephrectomy* was per-

formed *under local anesthesia* in 3 dogs.[†] The results are summarized in Table I and are identical with those obtained previously. A temporary hyperlipemia involving cholesterol, phospholipids, and total lipids was observed in all 3 animals. The highest values were obtained 4 to 8 days after operation with return to pre-operative levels after 10 to 14 days. It may be concluded that the general anesthesia used in former studies had no part in the development of the hyperlipemia following renal ablation.

When mercury bichloride was given by intramuscular or subcutaneous injection moderate tissue necrosis, resulting in ulcerations, was occasionally observed. It is conceivable that these lesions had an effect on the temporary hyperlipemia regularly observed after the administration of this nephrotoxic agent. *Mercury bichloride* therefore was given by *intravenous injection* in a 0.5% aqueous solu-

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¹ Heymann, Walter, and Clark, E. C., *Am. J. Dis. Child.*, 1945, **70**, 74.

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TABLE I.
Effect of Unilateral Nephrectomy, Performed Under Local Anesthesia, on Serum Lipids of 3 Dogs.

Dog No.	Avg preoperative values in mg%			Highest postoperative value in mg%			No. of days after operation
	Cholesterol	Lecithin	Total lipids	Cholesterol	Lecithin	Total lipids	
43	120	260	400	342	550	1050	6
44	160	300	580	253	370	800	8
40	200	350	600	255	540	880	4

TABLE II.
Effect of Intravenous Injection of Mercury Bichloride on Serum Lipids of Dogs.

Dog No.	Dose, mg/kg	Avg values before injection, mg%			Highest value after inj. in mg%			No. days after inj.
		Cholesterol	Lecithin	Total lipids	Cholesterol	Lecithin	Total lipids	
49	2	98	280	490	342	460	1100	4*
44	1	100	350	620	275	520	980	4
57	1.5	188	400	680	519	710	1180	5*
46	3	105	275	480	219	578	1080	2*
47	1	124	240	610	200	410	910	3

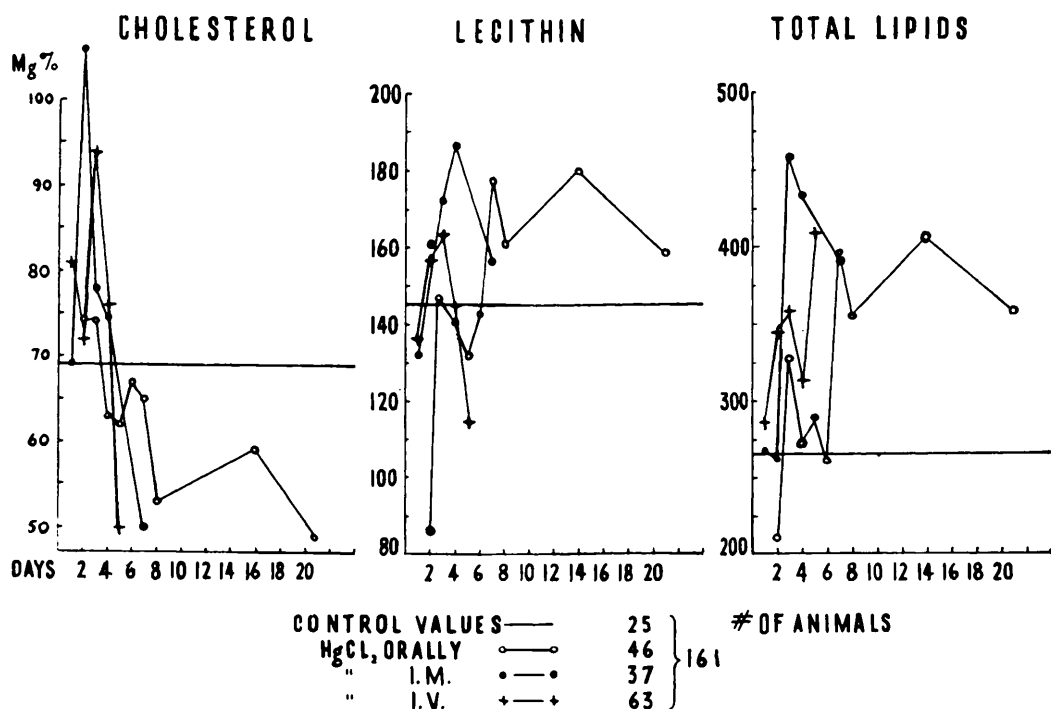
* Died same day.

tion to 5 dogs (Table II), thus avoiding local injury at the site of injection. The two animals injected with 1 mg mercury bichloride per kg body weight developed a transient hyperlipemia identical in pattern and intensity with the reaction observed when 5 mg per kg body weight had been injected under the skin or into the muscles. The 3 remaining dogs injected with 1.5, 2, and 3 mg per kg died within 5, 4, and 2 days respectively and a continuous increase of cholesterol, lecithin, and total lipids was observed in their serum. It thus is shown that the hyperlipemia described in former studies was due to the action of mercury bichloride, and was not dependent on the resulting local tissue necrosis.

Effect of Mercury Bichloride on Serum Lipids of Rats. The effect of subcutaneous injection of mercury bichloride on serum lipids of 15 rats has been reported previously.¹ Increased values had been found, but more extensive studies had to be carried out. Fig. 1 shows average values obtained in 161 animals. When given by stomach tube from 6 to 30 mg of mercury bichloride was given per 1000 g of body weight. By intramuscular injection a dose of from 5 to 7 mg was used, and intravenously only from 1 to 4 mg per 1000 g of body weight was injected. It is seen that after intramuscular and intravenous injection of mercury bichloride, cholesterol, lecithin, and total lipid values rise and descend within

the first 8 days. This immediate hyperlipemia is not observed when mercury bichloride is given orally. A delayed increase in lecithin and total lipids without corresponding rise of cholesterol values is observed, starting 7 to 8 days after its administration. These findings confirm the results obtained in dogs and it remains to be explained why in dogs and rats the oral administration of mercury bichloride is not followed by hyperlipemia, which is regularly observed when this agent is given by parenteral injection.

Effect of Carbon Tetrachloride on Serum Lipids of Dogs. Outside of renal ablation and tubular damage induced by nephrotoxic substances, severe tissue necrosis in dogs had been found to be followed by an identical hyperlipemia. One of the methods used to produce tissue necrosis had been the intramuscular injection of carbon tetrachloride which regularly led to the formation of severe abscesses. It had been concluded that not carbon tetrachloride, but the resulting necrosis of the tissues into which it had been injected was the cause for the increase in blood lipids. In order to test the validity of this conclusion, 15 cc of carbon tetrachloride was given by stomach tube to 2 dogs once, and 5 cc every 2 to 4 days to 4 dogs. The results are summarized in Table III. They show clearly that the oral administration of carbon tetrachloride decreased the concentration of cholesterol



BLOOD LIPIDS IN RATS AFTER ADMINISTRATION OF HgCl₂ (AVERAGE VALUES)

FIG. 1.

TABLE III.
Effect of Oral Administration of Carbon Tetrachloride on Serum Lipids of Dogs.

Dog No.	Avg values before administration of CCl ₄ in mg%			Lowest value after administration of CCl ₄ in mg%			No. days after first dose cc		Dose
	Cholesterol	Lecithin	Total lipids	Cholesterol	Lecithin	Total lipids			
31	115	260	490	100	220	450	14	15	once
33	188	300	680	100	220	580	13	15	"
60	118	200	400	72	130	300	4	5	every other day
56	131	330	550	50	130	320	21	5	" 2-4 "
47	148	340	520	50	150	120	25	5	" 2-3 "
44	190	374	630	49	150	350	24	5	" 2 "

lecithin, and total lipids in serum. This strongly suggests that the hyperlipemia previously observed was not due to carbon tetrachloride but to the tissue necrosis resulting from its intramuscular injection. The hypolipemia observed after its oral administration may well be connected with the hepatic damage so produced.

Summary and Conclusions. (1) Unilateral nephrectomy was performed under local anes-

thesia in 3 dogs and was followed by a transient hyperlipemia involving cholesterol, lecithin, and total lipids. It thus is shown that the general anesthesia used in previous studies had no part in the development of the hyperlipemia following renal ablation.

(2) Mercury bichloride given by intravenous injection to 5 dogs produced in all animals a hyperlipemia identical in pattern and intensity with the reaction observed when intramuscular or subcutaneous injections had