peared to be a shift in the metabolism of tyrosine. The type of curves (Fig. 2) suggest impaired liver function, but it is more likely that the shift represents a reduced rate of utilization of this amino acid for protein synthesis in contrast to an increased utilization prior to delivery. This is in keeping with the well-known transition from a positive to a negative nitrogen balance after delivery. In the two subjects tested only 1 and 3 hours post-partum, the blood values were still rising at 90 minutes, suggesting a delayed absorption. This may represent a persistence of the known delay in both stomach emptying time and absorption of foodstuffs during active labor. The fact that pregnancy and the puerperium alter the tyrosine tolerance curves in opposite directions from the normal, and the failure to find further alterations in the 2 severe toxemia cases, would make it hazardous to use this procedure as a liver function test in pregnant or puerperal women.

Conclusions. 1. The fasting blood tyrosyl level is significantly lowered during normal pregnancy, but not in the puerperium.

2. The reduced tyrosine tolerance curve during pregnancy suggests an increased rate of metabolism for this amino acid. There is an immediate reversal of this effect after delivery.

3. Unlike histidine, the renal tubular reabsorption of tyrosine appears to be as complete in pregnant as in non-pregnant subjects.

4. No alterations in tyrosine tolerance were noted in a case of preeclampsia nor in a case of eclampsia.

5. The observed shifts in tyrosine metabolism, possibly concerned with similar shifts in rates of protein synthesis, would probably invalidate the tyrosine tolerance test as a measure of liver function in pregnant and puerperal women.

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Further Studies on Renal Hyperlipemia.*

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Previous work[1,2,3] has shown that in dogs and rats unilateral and bilateral nephrectomy and the parenteral administration of nephrotoxic agents like mercury bichloride, uranium nitrate and potassium dichromate are followed by an increased blood lipid concentration. This effect of bilateral renal ablation has been confirmed by Winkler and associates[4] in dogs, has been recorded by these authors in monkeys, and by Nekludow[5] in cats. Hyperlipemia has also been found in rats made experimentally nephritic either by injection of antikidney serum[6] or by immunization with streptococcus—kidney antigen.[7] Hence, the kidneys of dogs, cats, rats and monkeys seem to function as part of a mechanism which influences blood lipid concentration.

Whether hyperlipemia also follows nephrectomy or renal injury in human beings has been investigated, and animal experiments have been carried out in an attempt

* Aided by a grant from the John and Mary R. Markle Foundation.

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4 Winkler, A. W., Durlacher, S. H., Hoff, H. E., and Mann, E. B., *J. Exp. Med.*, 1943, **77**, 473.

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6 Farr, L. E., Smadel, J. E., and Holden, R. F., Jr., PROC. SOC. EXP. BIOL. AND MED., 1942, **51**, 178

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TABLE I.
Effect of Unilateral Nephrectomy on Serum Lipids in Man.

	Cholesterol		Total lipids	
	Lowest value Mg %	Highest value	Lowest value Mg %	Highest value
Before Nephrectomy	151	190	400	540
After "	129	200	310	560
Before "	114	182	490	650
After "	114	191	490	800
Before "	191	238	800	930
After "	102	237	700	930

TABLE II.
Effect of Oral Administration of Mercury Bichloride on Serum Lipids in Man.

Dose in g	Cholesterol, mg %		Total lipids, mg %		Lecithin, mg %	
	Lowest value	Highest value	Lowest value	Highest value	Lowest value	Highest value
1.0	210	258				
1.0	85	160	440	720		
2.0	52	100	290	400	136	223
3.0	100	116	370	490	167	186
2.5	35	150	470	620	173	221
2.5	180	272				

to clarify the mechanism of the hyperlipemia.

Methods. Cholesterol analyses were made according to Schoenheimer and Sperry's method[8] which had been adapted to use with a photoelectric colorimeter.[9] The total lipids were analyzed according to the gravimetric method of Wilson and Hammer;[10] phospholipids were determined after extraction according to the technic of Bloor, with the method of Benedict and Theis[11] and were calculated as lecithin.

Effect of Unilateral Nephrectomy on Serum lipids in Man. Three patients with hydronephrosis, pyohydronephrosis and renal tuberculosis, respectively, were subjected to unilateral nephrectomy. During a period of 4 to 8 days before operation, determinations of total lipids and total and free serum cholesterol were carried out 2 to 4 times and daily for 2 to 3 weeks after the removal of one kidney. (Table I) No postoperative hyperlipemia was observed.

Effect of Mercury Bichloride Poisoning on Serum Lipids in Man. Total lipid, cholesterol and phospholipid determinations were carried out each day or every other day for 5 to 14 days on the sera of 6 patients who had taken mercury bichloride orally. Four of the 6 suffered severe kidney damage and died of uremia. Table II shows that all of the lipid values were normal or low. The observations thus failed to confirm the results of Wichert, Jakowlewa and Pospeloff[12] who found high cholesterol values in the blood of 2 patients poisoned with mercury bichloride.

Effect of Repeated Intravenous Infusions on the Hyperlipemia observed in Dogs After Unilateral Nephrectomy. Because the 3 nephrectomized patients had received, after their operations, an intravenous infusion of 1000 cc of Ringer's solution and 1000 cc of 5% glucose solution, we investigated the effect in dogs of such infusions upon the development of the post-nephrectomy hyperlipemia. Three dogs were unilaterally nephrectomized†

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11 Benedict, S. R., and Theis, R. C., *J. Biol. Chem.*, 1924, **61**, 63.

12 Wichert, M., Jakowlewa, A., and Pospeloff, S., *Z. f. klin. Med.*, 1924, **101**, 173.

†We are greatly indebted to Dr. Harry Goldblatt of the Institute of Pathology, Western Reserve University, School of Medicine, for performing the operations on the dogs.

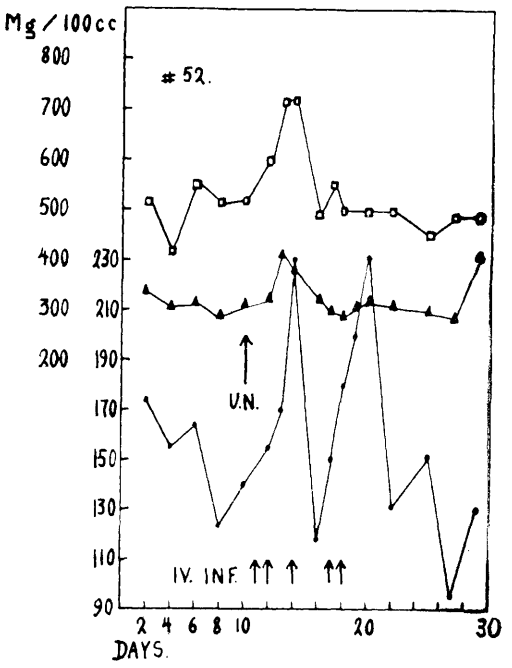

FIG. 1.

Effect of intravenous infusions of equal parts of Ringer's and 5% glucose solutions on serum lipids after unilateral nephrectomy in one of 3 dogs.

U. N., Unilateral nephrectomy.

Iv. Inf., Intravenous infusions.

Total Lipids, □——□

Lecithin, ▲——▲

Cholesterol, ●——●

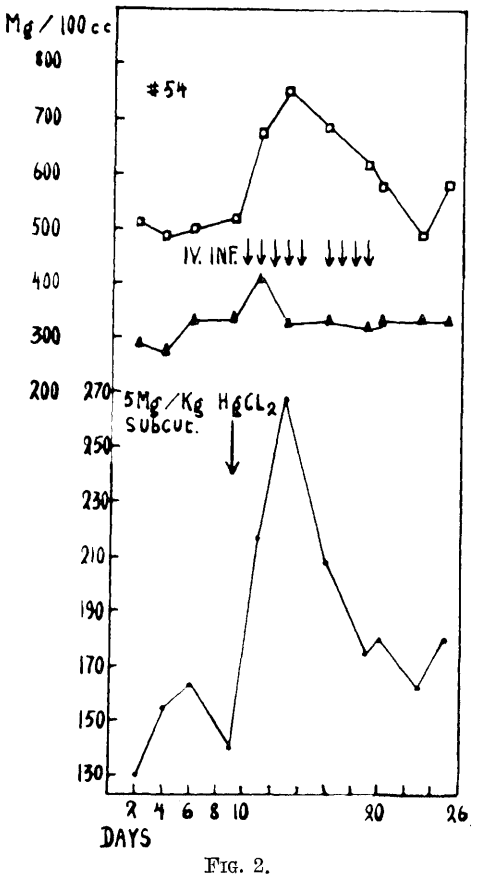

FIG. 2.

Effect of intravenous infusions of equal parts of Ringer's and 5% glucose solutions on hyperlipemia following injection of mercury bichloride in one of 3 dogs.

Iv. Inf., Intravenous infusions.

Total Lipids, □——□

Lecithin, ▲——▲

Cholesterol, ●——●

and given intravenous infusions every day or two after operation. Per kg body weight, 20 to 50 cc of equal parts of Ringer's and 5% glucose solution, were infused as in the nephrectomized patients. The infusion was by continuous intravenous drip for 1½ to 2 hours between 9 and 11 a.m. Blood samples were obtained for analysis before the infusions were started. Comparison of the results (Fig. 1) with those previously obtained[1,2] showed that the intravenous administration of the Ringer's and the glucose did not abolish, but did limit the extent of the post nephrectomy hyperlipemia. The changes in cholesterol, lecithin, and total lipid values observed were irregular and less marked in the dogs that received fluids after operation.

Effect of Repeated Intravenous Infusions on Hyperlipemia Observed in Dogs after Parenteral Administration of Mercury Bichloride. The effect of daily infusions on blood lipids was also studied in 3 dogs injected subcutaneously with 5 mg per kg body weight of mercury bichloride one day previous to the first infusion. Fig II shows that the infusions had little influence on the hyperlipemia development.

Effect of Repeated Oral Administration of Carbon Tetrachloride on Hyperlipemia Observed in Dogs after Subcutaneous Injection of Mercury Bichloride. In dogs and rats the oral administration of mercury bichloride had been previously shown[1,2] not to induce the hyperlipemia regularly observed after its parenteral administration. In both instances renal injury is produced. Inasmuch as mercury

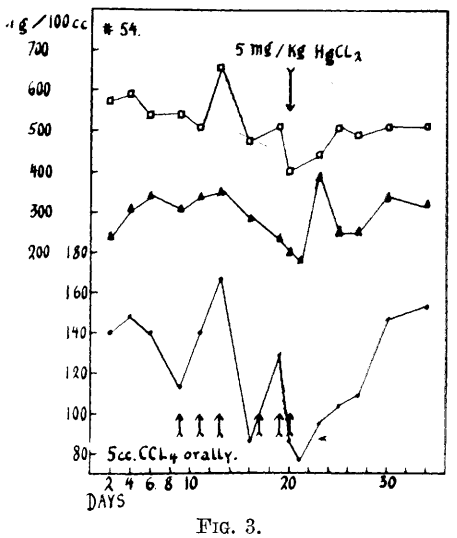

FIG. 3.

Effect on serum lipids in one of 3 dogs given carbon tetrachloride by stomach tube previous to a subcutaneous injection of mercury bichloride.
Total Lipids, □——□
Lecithin, ▲——▲
Cholesterol, ●——●

bichloride absorbed into the portal circulation might influence liver function, the effect of oral administration of carbon tetrachloride on the development of hyperlipemia was studied in dogs injected with mercury bichloride. After 5 cc of carbon tetrachloride had been given to 3 dogs by stomach tube at 2 to 4 day intervals for 12 to 18 days, 5 mg of mercury bichloride were injected subcutaneously. No elevation in blood lipid values was found in 2 of the dogs (Fig. 3). In the third, only a slight, delayed and irregular increase in total lipids and cholesterol was observed, and the phospholipids remained unchanged. The administration of carbon tetrachloride had thus inhibited the development of hyperlipemia otherwise observed after parenteral administration of mercury bichloride.

Discussion. The hyperlipemia observed in dogs after unilateral nephrectomy was not found in 3 human beings in whom one diseased kidney had to be removed. Although the conditions varied in the two series, it seems unlikely that the disparity is attributable to intravenous administration of fluids to the 3 nephrectomized patients after the operation. A possible explanation is that in the dogs, healthy kidneys were removed, whereas the kidneys removed from the 3 patients were severely diseased. In 2 of the 3 patients, two-thirds of the removed kidneys seemed to be intact, but only 2 to 3mm of cortex was left in the 3rd kidney. Unimpaired anatomical structure of about two-thirds of renal tissue, however, does not imply functional integrity. Welsh, Mellin and Taylor[13] have shown that certain functional changes accompanying the renal hypertrophy which follows unilateral nephrectomy in human beings, are not observed when the removed kidney is severely diseased.

In dogs and rats the parenteral administration of mercury bichloride is regularly followed by hyperlipemia. This is not the case, however, when the mercury bichloride is given by stomach tube. The results of oral administration in human beings are in agreement with those obtained in animals given mercury bichloride by stomach tube. Why hyperlipemia develops only after parenteral and not after enteral administration of mercury bichloride, despite the fact that renal injury is produced in both instances, remains to be clarified. Suggestive evidence was obtained that liver function could interfere with the development of hyperlipemia. Liver injury, produced experimentally by carbon tetrachloride in 3 dogs, inhibited the development of the hyperlipemia otherwise regularly observed after the parenteral administration of mercury bichloride.

Summary. 1. Determinations of total lipids, total and free cholesterol were carried out in 3 patients subjected to unilateral nephrectomy. No hyperlipemia was observed.

2. Total lipids, cholesterol and phospholipids were determined in the serum of 6 patients with mercury bichloride poisoning. The values were normal or low.

3. Daily intravenous infusions of equal parts of 5% glucose and saline solution in dogs after unilateral nephrectomy and subcutaneous injection of mercury bichloride had some influence on the post nephrectomy hyperlipemia.

13 Walsh, G. A., Mellin, L., and Taylor, H. C., Jr., *J. Clin. Invest.*, 1944, **23**, 750.

4. Repeated oral administration of carbon tetrachloride prior to the subcutaneous injection of mercury bichloride in 3 dogs prevented the hyperlipemia in 2 of the animals.

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Hyperglycemia Induced by Certain Insulin Preparations.*

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In an attempt to demonstrate electroencephalographic changes characteristic of hypoglycemia, a preparation of insulin was injected intravenously into a paralyzed, artificially respirated cat at 30-minute intervals, the initial dose being one unit per kg body weight and each subsequent dose twice that of the preceding one. Four hours after the initial dose, no change in the electroencephalogram was evident. In similar experiments a transitory increase in blood glucose concentration usually followed each injection of insulin and hypoglycemia did not develop.

Since the cats used in the experiments considered above were paralyzed with dihydro-β-erythroidine hydrobromide and the blood glucose levels were high, the effect of intravenous injection of insulin preparations on the concentration of blood glucose was tested in anesthetized (amytal) and intact cats. Representative data are given in Tables I and II. In addition to the experiments summarized in the tables, others were carried out in which different times of collection of blood were used, no injection was made, other preparations of amorphous insulin were used, arterial blood was assayed, doses of insulin intermediate to and greater than those indicated were employed, and in which insulin was given subcutaneously and intramuscularly. The effect of intravenous injection of insulin during hypoglycemia, induced by insulin, and hyperglycemia, induced by administration of glucose, was also tested.

The results of the experiments may be summarized as follows. Intravenous injection of water or salt solution in volumes comparable to the volumes of insulin used provoked no marked change, or certainly no consistent change, in blood glucose level. With intravenous injection of all preparations of insulin tested (except NOVO) the blood glucose concentration increased, the maximum occurring 5-10 minutes after injection. The glucose concentration returned to the control level 20-30 minutes after injection at which time hypoglycemia began to develop. The increase in glucose concentration was evident with 0.1 unit of insulin per kg body weight and marked with one unit. The hyperglycemic effect seemed to be somewhat more pronounced in the anesthetized than in the intact or paralyzed cat.

The effect was apparently independent of the blood glucose level, *e.g.* intravenous injection of 2 units of a preparation of crystalline zinc insulin per kg when, after intramuscular administration of insulin, the blood glucose level was gradually falling and had reached 18 mg per 100 ml, was followed by an increase in glucose level to 82 mg per 100 ml and disappearance of electroencephalographic changes characteristic of hypoglycemia; likewise, intravenous injection of insulin, at high blood glucose levels, induced by administration of glucose, was followed by increases in glucose level. With subcutaneous and intramuscular administration of the several preparations of insulin no increase in blood glucose level occurred.

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