

PLASMA LIPID INTERRELATIONSHIPS IN EXPERIMENTAL NEPHROSIS¹

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(Submitted for publication May 7, 1957; accepted July 11, 1957)

The injection of rabbit anti-rat kidney serum induces a nephrotic state in rats which closely resembles that occurring in human subjects with the nephrotic syndrome (1). Earlier studies from this laboratory (2-7) indicated that the increase of plasma lipids which occurs in the nephrotic rat's plasma is primarily due to an intravascular "trapping" phenomenon whereby the animal is unable to clear lipid from the plasma with his customary efficiency. It also was found (8, 9) that the profound deficiency of albumin characteristic of the nephrotic rat's plasma appears to be causally responsible for this retention of excess lipid in his plasma. A contributing factor may be the renal loss of heparin or its plasma equivalent, lipoprotein lipase (10). However, the sequential mechanism whereby the deficiency of albumin, and possibly also of lipoprotein lipase in nephrotic plasma, initiates and maintains the increased plasma content of all lipid fractions, remains to be elucidated. This problem has been investigated in the present studies.

METHODS AND RESULTS

Young adult, male rats of the Long-Evans strain (weight, 190 to 225 Gm.) were used in the following studies. Rabbit anti-rat kidney serum (AKS) was prepared by the method of Heymann and Lund (1). Where designated, continuous intravenous infusion was accomplished by means of a special constant infusion apparatus connected to a polyethylene cannula in an inferior lumbar vein, as described previously (8). The studies were performed after an overnight fast, and food was withheld during the experimental intervals.

I. The serial interrelationships of the plasma lipid changes in rats injected with AKS

Methods

A. One ml. of pooled AKS was injected into each of 120 rats. At serial intervals during the ensuing 168 hours a separate group of 10 rats was sacrificed and bled from

¹ Aided by grants from the National Institutes of Health, Public Health Service, Grant A-1213, the American Heart Association and the San Francisco Heart Association.

the aorta for determination of plasma albumin (8), total lipids (9), phospholipids (10) and total cholesterol (11). Plasma triglycerides were calculated by difference (subtracting total cholesterol and phospholipids from total lipid). Each rat was bled only once, to avoid the effects of serial sampling. Control values were established in an additional group of 25 normal rats.

B. In order to evaluate further the initial plasma lipid changes induced by AKS injection, an additional series of 20 rats was injected with 1.2 ml. of pooled AKS. Seven of the rats were sacrificed five hours later and the remaining 13 rats eight hours after AKS injection, at which time the rats were bled from the aorta for determination of plasma albumin, total lipids, phospholipids, and total cholesterol.

Results

A. In Figure 1 it can be seen that the injection of AKS in the first series of rats induced a progressive fall of plasma albumin which preceded the rise of plasma lipids. Thus the plasma albumin fell from an initial average of 3.1 Gm. per 100 ml. to an average of 0.5 Gm. per 100 ml. at 24 hours, a level which prevailed throughout the remainder of the experimental interval. There was a parallel rise and later partial fall of plasma phospholipids and total cholesterol. Therefore, for purposes of illustration the concentrations of phospholipids and cholesterol have been combined in Figure 1 in which the plasma triglycerides are represented by the difference between the average concentrations of total lipids and those of the combined cholesterol and phospholipids. It can be seen that, although there was a progressive rise of all three plasma lipid fractions, the rise of plasma triglycerides occurred at a more rapid rate and was of considerably greater magnitude than that of the other lipid fractions. After reaching a peak rise at 96 hours a partial fall of the elevated lipid levels occurred, during which it was observed that the plasma triglycerides fell much more rapidly than did the other lipid fractions.

B. The results of the second series of rats are presented in Figure 2 in which it can be noted that

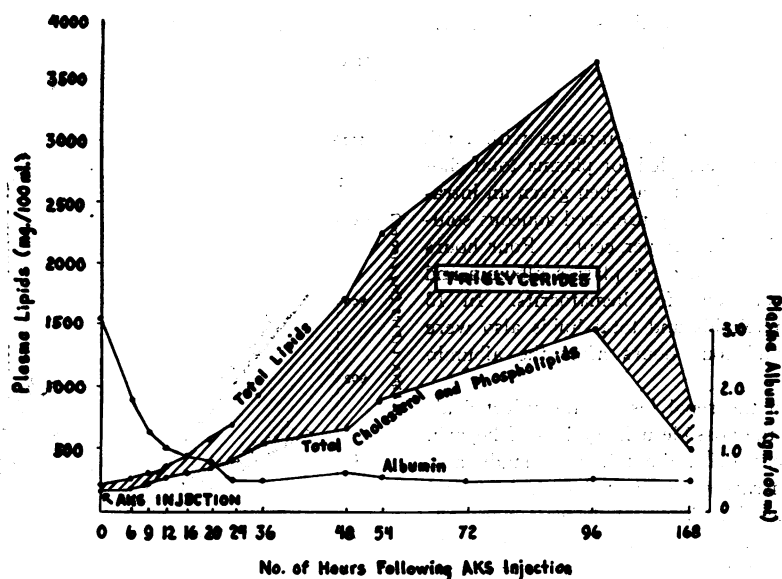


FIG. 1. THE TEMPORAL RISE OF PLASMA LIPIDS IN RATS INJECTED WITH ANTI-KIDNEY SERUM

a progressive fall of plasma albumin and associated rise of plasma lipids again was induced by AKS injection. As shown in Figure 2, triglyceride was the first plasma lipid fraction to rise following AKS injection. Thus, five hours after AKS injection, the plasma triglycerides had risen from an initial average of 20 mg. per 100 ml. to 53 mg. per 100 ml. At the same time no significant change of average plasma cholesterol or phospholipid was observed. Eight hours after AKS injection the plasma triglycerides rose further, to an average of 110 mg. per 100 ml., at which time a slight rise of plasma phospholipid but no change

of plasma cholesterol was observed. The range of values and statistical evaluation also are shown in Figure 2.

II. The fall of plasma lipids in nephrotic rats injected with albumin

The results of the previous experiment were consistent with the concept (8, 12, 13) that a preceding accumulation of plasma triglycerides is the factor initiating and sustaining the rise of the other plasma lipid fractions. However, if this concept were valid it would be expected that, during the fall of the elevated plasma lipids previously shown to occur in nephrotic rats following injection of albumin (8, 12, 13), the plasma triglycerides would fall at a more rapid rate than would the concentra-

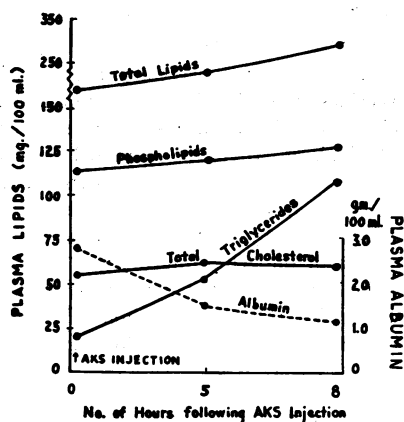


FIG. 2. THE INITIAL PLASMA LIPID CHANGES IN RATS INJECTED WITH ANTI-KIDNEY SERUM

	No. of Hours		
	0	5	8
TOTAL LIPIDS	191	235	303
Range:	(135-225)	(203-262)	(250-380)
S.E. Mean:	±9.0	±7.3	±9.2
TRIGLYCERIDES	20	53	110
Range:	(0-44)	(30-74)	(76-165)
S.E. Mean:	±3.9	±5.0	±7.5
PHOSPHOLIPIDS	114	121	130
Range:	(83-130)	(112-138)	(111-154)
S.E. Mean:	±3.6	±4.0	±3.3
TOTAL CHOLESTEROL	56	63	62
Range:	(40-69)	(46-74)	(44-72)
S.E. Mean:	±2.1	±3.9	±2.0

tions of cholesterol and phospholipids. This problem was studied in the next experiments.

Methods

A. Each of a series of 24 rats was injected with 1 ml. of pooled AKS. The rats were bled for plasma total cholesterol 72 hours later. Each rat was then given an intravenous injection of 3 ml. of freshly prepared aqueous solution of bovine serum albumin (25 per cent). Four hours later the animals again were bled for plasma albumin and cholesterol concentrations and for hematocrits. In 13 instances plasma phospholipids and total lipids also were determined prior to and four hours after the albumin injection.

B. In order to avoid the renal loss of the injected albumin (8), as well as the possible urinary loss of heparin or its plasma equivalent (12), the following study also was performed. Seven rats were injected with AKS and five days later were bled for plasma cholesterol, phospholipids, and total lipids. Each rat was then subjected to bilateral nephrectomy through dorsal incisions and then injected intravenously with 3 ml. of 25 per cent solution of bovine serum albumin. Four hours later the rats were bled for plasma albumin, hematocrits, total lipids, phospholipids and total cholesterol.

Results

A. The average fall of the plasma lipid fractions induced by albumin injection in the intact rats is shown in Figure 3, A. The plasma triglyceride concentration fell from an initial average of 816 mg. per 100 ml. to 270 mg. per 100 ml., a fall of 67 per cent. The plasma phospholipids exhibited a 55 per cent fall from an initial average of 467 mg. per 100 ml. to 211 mg. per 100 ml., and the plasma total cholesterol a 56 per cent fall from an initial average of 295 mg. per 100 ml. to 129 mg. per 100 ml. At the time of the final bleeding the average plasma albumin concentration was 2.9 Gm. per 100 ml. (range, 1.2 to 4.6) and the average hematocrit was 36 (range, 31 to 39).

B. The second series of rats was studied at a later interval following AKS injection than in the previous group and a considerably more intense hyperlipemia was observed at the time of the first bleeding (Figure 3, B). As the probable result of preventing urinary loss of the injected albumin and possibly also of heparin or of lipoprotein lipase (8, 12), a more marked fall of plasma lipids was observed following injection of albumin than occurred in the preceding experiment. Thus, a 93 per cent average fall of plasma triglyceride occurred, from an initial average of 1,866 mg. per

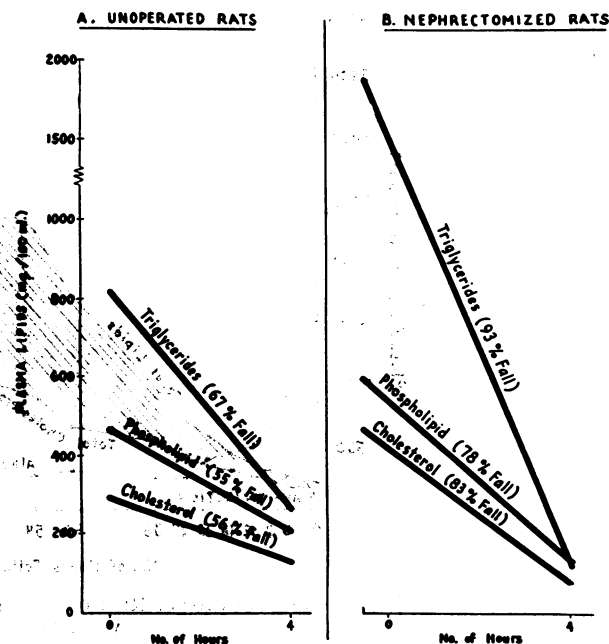


FIG. 3. THE FALL OF PLASMA LIPIDS IN CHRONIC NEPHROTIC RATS INJECTED WITH ALBUMIN

100 ml. to 124 mg. per 100 ml. As in the first series of rats, a relatively lesser fall of the other plasma lipids was observed. Thus the plasma cholesterol fell an average of 83 per cent, from an initial average of 470 mg. per 100 ml. to 78 mg. per 100 ml., and the phospholipids fell an average of 78 per cent, from an initial average of 598 mg. per 100 ml. to 133 mg. per 100 ml. At the time of the final bleeding the plasma albumin averaged 5.5 Gm. per 100 ml. (range, 5.1 to 5.8) and the average hematocrit was 28 (range, 22 to 32).

III. The effect of fat infusion and of Triton injection on the plasma lipids of rats injected with AKS

In the event that a preceding accumulation of plasma triglycerides in nephrotic plasma initiated and sustained the observed subsequent rise of plasma cholesterol and phospholipid, it would be expected that an associated further increase of plasma cholesterol and phospholipid would occur if an additional increment of excess triglyceride, given by continuous infusion, was retained in the plasma of the AKS-injected rat. A similar sequence would be expected if the hypertriglyceridemia was augmented by the injection of Triton WR-1339 (14). This problem was studied in the following experiments.

Methods

A. Each of 30 rats was injected with 0.6 ml. of pooled AKS, an amount which was found in preliminary studies to be inadequate to induce any significant rise of plasma

lipids during the ensuing five-hour interval. The rats then were prepared for continuous intravenous infusion and, during the subsequent five-hour interval, 10 of the rats were infused continuously with 6.0 ml. of fat² and, for control purposes, the remaining 20 rats were infused with 6.0 ml. of sodium chloride solution (0.9 per cent). The animals then were bled from the aorta for determination of plasma albumin, total lipids, total cholesterol and phospholipids.

B. A second series of 13 rats was also injected with AKS, but 24 hours elapsed before the experimental interval. At that time the rats were bled for plasma total cholesterol and total lipids. The rats were then continuously infused for five hours, five being injected with 6.0 ml. of triglyceride, and the remaining eight control rats receiving a similar amount of saline solution. All rats were bled at the end of the infusion interval for plasma albumin, total lipids, total cholesterol and phospholipids.

C. A series of 10 rats was injected with 1 ml. of AKS. Fifty hours later the rats were bled for determination of plasma total lipids, phospholipid, and total cholesterol and found to be hyperlipemic. Five of the rats were then injected intravenously with 100 mg. of Triton WR-1339 (contained in 1 ml.), the remaining rats serving as controls. All rats were bled 24 hours later for plasma total lipids, phospholipid, and total cholesterol.

Results

A. The results obtained in the first series of rats are shown in Figure 4, A. In the five hours following injection of the smaller amount of AKS only an occasional saline-infused control rat developed any significant increase of plasma lipids: the average plasma triglycerides was 52 mg. per 100 ml.; average plasma cholesterol, 72 mg. per 100 ml.; and the average plasma phospholipids, 132 mg. per 100 ml. As shown in Figure 4, A, the rats infused with triglyceride exhibited considerably higher plasma triglyceride concentrations, which averaged 635 mg. per 100 ml. In association with this induced hypertriglyceridemia, a rise of plasma cholesterol (average, 115 mg. per 100 ml.) and of phospholipids (average, 220 mg. per 100 ml.) was observed. Comparable average plasma albumin concentrations of 1.4 and 1.5 Gm. per 100 ml. were observed in the two groups of rats.

B. The rats of the second series were initially

² Lipid emulsion (kindly furnished by Don Baxter) composed of sesame oil, USP, 10; dextrose, USP, 4.5; purified soya bean lecithin, 0.65; water, q.s. 100 ml. Lipid is present as finely divided particles of 1 μ or less in diameter.

bled 24 hours after AKS injection, at which time the controls exhibited average plasma total lipids of 445 mg. per 100 ml. (range, 397 to 514) and plasma total cholesterol of 114 mg. per 100 ml. (range, 93 to 131), and the experimental group exhibited average plasma total lipids of 432 mg. per 100 ml. (range, 410 to 481) and cholesterol of 108 mg. per 100 ml. (range, 99 to 120). At the end of the ensuing five-hour infusion interval the saline-injected controls (Figure 4, B) exhibited average plasma triglycerides of 126 mg. per 100 ml., phospholipids of 196 mg. per 100 ml., and total cholesterol of 128 mg. per 100 ml. A marked increase of plasma triglycerides, averaging 2,497 mg. per 100 ml., was induced in the rats infused with triglyceride. In these rats considerably increased plasma concentrations of cholesterol and phospholipids also were observed, respectively averaging 226 mg. per 100 ml. and 364 mg. per 100 ml. Comparable average plasma albumin levels of 0.6 and 0.5 Gm. per 100 ml. were observed in the two groups of rats.

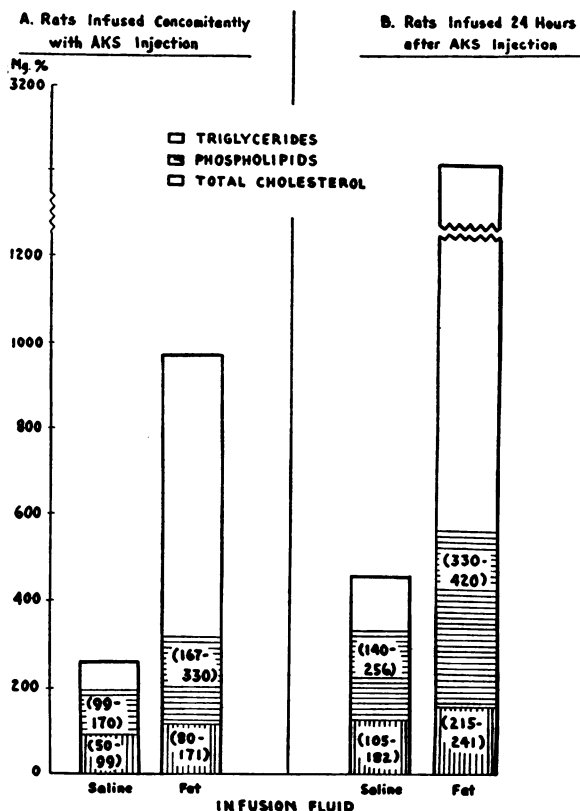


FIG. 4. THE EFFECT OF FAT INFUSION ON PLASMA LIPIDS OF RATS INJECTED WITH AKS

C. A marked further rise of plasma lipids and cholesterol occurred in the nephrotic rats during the 24-hour interval following injection of Triton. Thus the plasma total lipids of the Triton-injected nephrotic rats rose from an average of 2,280 mg. per 100 ml. (range, 1,560 to 3,400) to 4,713 mg. per 100 ml. (range, 4,349 to 5,180), the plasma triglyceride rose from an average of 1,197 mg. per 100 ml. (range, 747 to 2,113) to 2,610 mg. per 100 ml. (range, 2,467 to 3,034). The plasma cholesterol rose from an average of 393 mg. per 100 ml. (range, 278 to 462) to 805 mg. per 100 ml. (range, 712 to 874) and the plasma phospholipid rose from an average of 690 mg. per 100 ml. (range, 535 to 825) to 1,298 mg. per 100 ml. (range, 1,090 to 1,272). At the same time the average plasma total lipids of the control group rose from an average of 1,547 mg. per 100 ml. (range, 1,287 to 1,713) to 2,120 mg. per 100 ml. (range, 1,591 to 2,490), the plasma cholesterol rose from an average of 411 mg. per 100 ml. (range, 264 to 487) to 518 mg. per 100 ml. (range, 432 to 538) and the plasma phospholipid rose from an average of 520 mg. per 100 ml. (range, 462 to 589) to 632 mg. per 100 ml. (range, 581 to 689).

IV. The effect of phospholipid infusion on the plasma cholesterol of AKS-injected rats

In the preceding studies it was found that a rise of plasma cholesterol occurred when sustained hypertriglyceridemia was induced by injection of AKS and that the magnitude of the hypercholesteremia was proportionately increased when the degree of hypertriglyceridemia in such rats was augmented by the infusion of triglyceride or by injection of Triton. However, a rise of plasma phospholipids also occurred in such animals. On the other hand, the rise of phospholipids and of cholesterol was of such similar nature that it was difficult if not impossible to determine whether a causal relationship existed between these lipid fractions. It appeared of importance, however, to evaluate the possible role of induced hyperphospholipemia in the rise of plasma cholesterol which occurs in AKS-injected rats, in view of the recent observations in this laboratory (15, 16) that a rise of plasma cholesterol occurs in normal rats in which sustained hyperphospholipemia is induced by the continuous infusion of phospholipids. This problem was therefore studied in the following experiments.

Methods

A. The sequential rise of plasma cholesterol and phospholipids induced by AKS injection was studied by injecting each of a series of 53 rats with 1 ml. of pooled

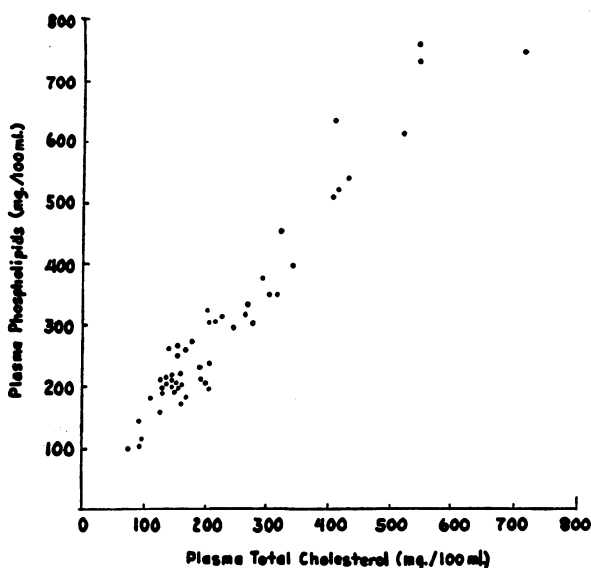


FIG. 5. CORRELATION OF PLASMA PHOSPHOLIPIDS AND TOTAL CHOLESTEROL IN RATS INJECTED WITH ANTI-KIDNEY SERUM

AKS. Groups of 10 to 11 rats were then bled for plasma total cholesterol and phospholipids at 8, 15, 24, 48 and 96 hours following the injection of AKS.

B. The effect of phospholipid infusion in AKS-injected rats was studied in the next experiment. One ml. of pooled AKS was injected into each of 18 rats. During the ensuing 24-hour interval, seven of the rats were continuously infused intravenously with 12 ml. of 2 per cent solution of phospholipids.⁸ For control purposes a comparable amount of glucose solution (5 per cent) was infused into six others. The rats were bled for plasma total lipids, total cholesterol and phospholipids at the end of the 24-hour infusion interval.

The remaining five rats were not studied until 20 hours after AKS-injection, at which time they were continuously infused during the ensuing 24-hour interval with 12 ml. of 2 per cent phospholipid solution.⁸ The rats were bled for plasma total lipids, total cholesterol and phospholipids prior to and following the infusion interval.

Results

A. A serial parallel rise of the concentrations of plasma cholesterol and phospholipids was induced by AKS injection, as occurred in the first experiment. In Figure 5 it can be seen that the induced rise of plasma total cholesterol in these rats was directly proportional to the rise of plasma phospholipids.

⁸ Furnished by Glidden Company as "Soya Lecithin" (RG) brand and dissolved in 5 per cent glucose solution.

B. In the second experiment certain rats were injected with AKS just prior to the continuous 24-hour infusion of phosphatide or glucose. At the end of the infusion interval the rats injected with phosphatide exhibited plasma total lipids averaging 1,012 mg. per 100 ml. (range, 756 to 1,200). There was a marked rise of plasma phospholipids averaging 703 mg. per 100 ml. (range, 522 to 924) and a much smaller rise of cholesterol averaging 213 mg. per 100 ml. (range, 173 to 286). In contrast, the glucose-infused controls exhibited average plasma total lipids of 382 mg. per 100 ml. (range, 350 to 466), average phospholipids of 189 mg. per 100 ml. (range, 148 to 199) and average total cholesterol of 142 mg. per 100 ml. (range, 130 to 148). Thus, no significant increase of plasma triglyceride was induced by the phosphatide infusion.

The remaining rats were injected with AKS 20 hours prior to the infusion of phosphatide. These rats exhibited a marked further rise of plasma phospholipids, from an initial average of 179 mg. per 100 ml. (range, 100 to 236) to 1,038 mg. per 100 ml. (range, 842 to 1,430). There was an associated but relatively much smaller rise of plasma cholesterol from an initial average of 150 mg. per 100 ml. (range, 77 to 208) to 382 mg. per 100 ml. (range, 342 to 396). The plasma total lipids averaged 1,620 mg. per 100 ml. (range, 1,290 to 1,830) at the end of the infusion interval.

DISCUSSION

The results of previous studies from this laboratory have indicated that the increase of lipids in the nephrotic rat is an isolated accumulation of excess lipids which is confined, at least in the early phase, to its plasma (4) and which, although capable of intensification by ingestion of dietary lipid (5), stems primarily from endogenous sources (5). Our studies also indicated that the accumulation of cholesterol in the plasma in this syndrome is not caused by any preceding change in its intestinal absorption (2) or excretion (3), or in the rate of its hepatic synthesis (6). Finally, it was found that both the hyperlipemia and the hypercholesteremia were initiated by the loss of albumin and, conversely, were remedied by the administration of albumin (8, 13) particularly in conjunction with heparin (12).

In the present studies further information was obtained concerning the causal mechanism involved in the hyperlipemia and hypercholesteremia occurring after induction of the nephrotic state. Thus, soon after injection of AKS, a profound fall of plasma albumin was found to occur and, concomitantly with this, the plasma triglyceride, of all the plasma lipid fractions, first begins to rise. It is likely that this retention of excess triglyceride in nephrotic plasma is due to a failure in its hydrolysis consequent to a deficiency of circulating albumin (8) and possibly also of lipoprotein lipase (13), since such lipolysis appears to be a prerequisite for the normal clearance of triglyceride from the plasma (17, 18). The initial rise of triglyceride was followed considerably later by a rise of both plasma phospholipid and cholesterol.

Earlier studies from this laboratory (15, 19) have demonstrated that an accumulation of excess triglyceride in the plasma of the normal rat quickly induces a subsequent rise both of plasma phospholipid and cholesterol. The results obtained in the present studies appear to indicate that a similar mechanism is in play in the nephrotic state. Thus the rise of triglyceride in the nephrotic rat's plasma was found to precede the rise of plasma phospholipid and cholesterol, and if the triglyceride content of the plasma was either reduced by albumin infusion or further elevated by infusion of triglyceride itself, or by Triton injection (14), a prompt fall or elevation, respectively, occurred in the plasma phospholipid and cholesterol concentrations. The pathogenesis of the hypercholesteremia and hyperphospholipemia occurring in nephrosis thus appears to be similar to that occurring after injection of the surface active substance, Triton WR-1339, which, similar to the injection of AKS, first produces a rise of triglyceride in the plasma (14). It would appear that the excess phospholipid and cholesterol accumulate in nephrotic plasma secondarily, perhaps as the result of their preferential solubility in the increment of excess triglyceride in the plasma (19-21).

As in Triton-induced hypercholesteremia (14), the rise and fall of cholesterol in nephrotic plasma occurred parallel with a rise and fall of plasma phospholipids. This suggested that the hyperphospholipemia did not play a major role in the

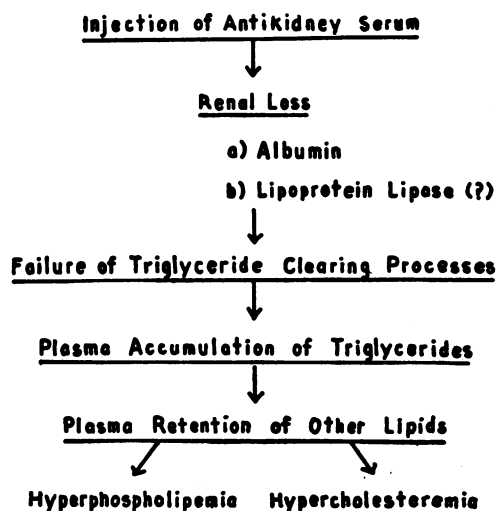


FIG. 6. PATHOGENESIS OF NEPHROTIC HYPERLIPEMIA AND HYPERCHOLESTEREMIA

retention of excess cholesterol in nephrotic plasma, despite the previously demonstrated ability (15, 16) of an induced rise of plasma phosphatide to effect a hypercholesteremia. Moreover, although a further rise of plasma cholesterol did occur in the nephrotic rat, as in the normal rat (15), when phosphatide was infused in an amount sufficient to further raise the plasma phospholipid concentration, the resulting plasma levels were notably disproportionate. Thus, the further rise of plasma cholesterol in such rats was of relatively much less magnitude than the marked induced rise of phospholipids. This could not be ascribed, however, to any inability of such rats to accumulate an additional increment of cholesterol in the plasma at a more rapid rate, since a considerably greater rise of cholesterol was observed in similar nephrotic rats during the infusion of triglyceride or following injection of Triton.

On the basis of the evidence cited above the pathogenesis of the accumulation of excess plasma lipids in experimental nephrosis may be summarized as shown in Figure 6.

SUMMARY

The sequential changes and the interrelationships among the plasma lipid fractions were studied in rats injected with anti-kidney serum, and in nephrotic rats infused with fat or with phosphatide. The results are consistent with the con-

cept that the AKS-induced deficiency of plasma albumin primarily induces an intravascular retention of plasma triglycerides. The accumulation of cholesterol and phospholipid in nephrotic plasma appears to be a passive derangement secondary to the lipid-sequestering properties of the increment of excess triglycerides in such plasma.

ACKNOWLEDGMENT

We wish to express our appreciation to Armour & Company for the generous supplies of bovine serum albumin provided for this study.

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