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The nature of the epinephrine-induced hyperlipidemia in dogs and its modification by glucose*

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SUMMARY

Dogs receiving subcutaneous epinephrine in oil (1 mg. per kg.) showed a prompt but transient elevation in serum free fatty acids (FFA) and a delayed 24-hour elevation of serum lipoproteins. On daily injections of epinephrine for 6 to 8 days the serum cholesterol rose to 91 per cent above control values and the phospholipid 53 per cent. The triglyceride response was smaller and quite variable. Little change was found in the $d < 1.019$ lipoprotein, a three to eightfold increase in the $d = 1.019$ to 1.063 fraction and a 15 to 41 per cent increase in the $d = 1.063$ to 1.21 fraction. Epinephrine prolonged alimentary lipidemia but did not inhibit disappearance of intravenously infused chylomicrons. By prior and concomitant administration of glucose the FFA elevation after epinephrine was prevented. Insulin alone also blocked the epinephrine-induced FFA response without parallel hyperglycemia, indicating that availability of glucose for effective tissue utilization rather than hyperglycemia per se controls the release of FFA. Despite the block in the FFA response to epinephrine by either glucose or insulin, there was a definite elevation of serum cholesterol and phospholipids at 24 hours, suggesting an at least partially independent lipoprotein mobilizing action of the hormone. The relation of these findings to stress-induced hypercholesterolemia is considered.

In 1928 Cori and Cori (1) showed that epinephrine-induced hypermetabolism was accompanied by a depression of the respiratory quotient, implying an increased utilization of fat. The nature and the mechanism of the lipid mobilization due to epinephrine, however, deserves re-examination in the light of recent advances in the field of fat metabolism.

In early investigations with aqueous epinephrine solutions, diverse or inconsistent changes in blood lipid levels were noted (2). More recently it has been reported that administration of long-acting epinephrine in oil causes a rise in serum cholesterol, phospholipids, and triglycerides of dogs and rabbits (3, 4). Epinephrine in aqueous solution has also been demonstrated to raise considerably the blood level of free fatty acids (FFA) in humans (5, 6) as well as to mobilize FFA from rat adipose tissue *in vitro* (7).

This investigation was carried out to determine the nature of the epinephrine-induced hyperlipidemia and to establish whether any relationship exists between the increases in circulating FFA and the elevation of other blood lipids following epinephrine administration.

METHODS AND EXPERIMENTAL PROCEDURES

Experiments were performed on mongrel dogs weighing 9 to 17 kg. They were maintained on a dry meal of 7 per cent fat content offered each morning for 4 hours. In the long-term studies six dogs received a single dose of 1 mg. per kg. epinephrine in peanut oil,[1]

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[1] Supplied by Dr. J. E. Gajewski of Parke, Davis and Co.

administered subcutaneously, daily at 9 A.M. for a period of 6 to 8 days. Venous blood samples were drawn after a 20-hour fast, just before the daily dose of epinephrine was given. The blood was promptly chilled and kept at 4°C until the analytical procedures were started, within 2 hours. In six fasting dogs changes in serum lipid constituents were measured during the 24 hours following a single injection of epinephrine in oil. For the sake of comparison, an equivalent amount of epinephrine in saline solution (Adrenalin Chloride®) was infused over a period of 5 hours to two fasting dogs anesthetized with Pentothal®.

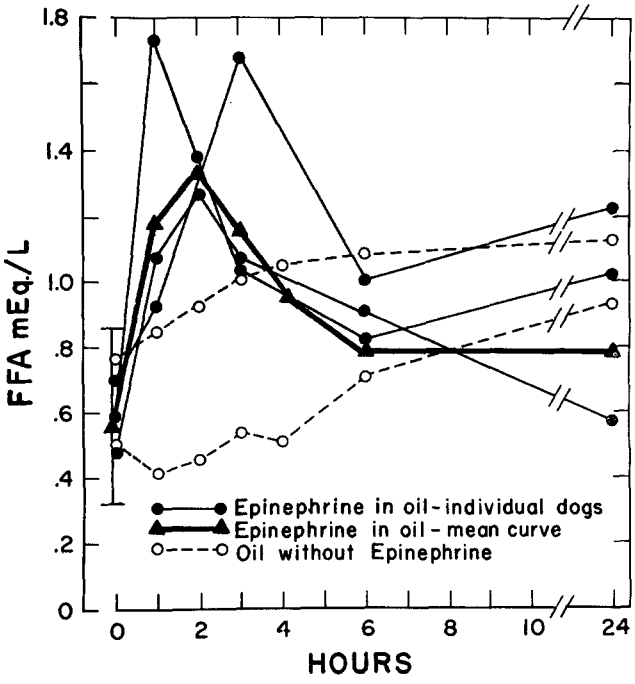

FIG. 1. Serum FFA levels during 24 hours following a single injection of epinephrine in oil. The vertical bar parallel to the ordinate indicates the range of normal fasting FFA values in 24 dogs used throughout this study.

In the fat load experiments, whipping cream was introduced by stomach tube or a specified amount of canned meat [2] was given to six fasting dogs and the serum lipid levels were determined at intervals over the following 24 hours. A week later the same animals received the fat load 30 minutes after a single subcutaneous dose of epinephrine in oil (1 mg. per kg.).

The rate of disappearance of intravenously injected chylomicrons was measured in untreated dogs and in the same dogs 30 minutes after subcutaneous injection of epinephrine in oil (1 mg. per kg.). Chylomicron disappearance was measured by a method similar to that described by Havel and Fredrickson (8). Thoracic duct chyle obtained from cream-fed donor dogs served as the source of chylomicrons. Chyle was injected into the external jugular vein of the recipient dogs under Pentothal® anesthesia in an amount representing 100 mg. triglyceride per kg. body weight. Blood samples were withdrawn at timed intervals from the femoral artery. The samples were delivered into heparinized tubes, kept on ice for 1 hour and centrifuged at approximately 1800 $\times$ g. The optical density of the supernatant whole plasma was read in a Coleman Junior spectrophotometer at a wave length of 660 mμ. It has been shown that the curves obtained by this simple procedure parallel those obtained when the chylomicrons are first isolated ultracentrifugally and then suspended in 0.9 per cent sodium chloride solution for the measurement of optical density or when chylomicron triglyceride content is determined.[3]

In the study of the effect of carbohydrate on epinephrine-induced 24-hour serum lipid changes, 30 g. of glucose in a 30 per cent aqueous solution was administered by stomach tube, followed by five doses of 15 g. each, at 30-minute intervals. Immediately after the second dose, the dog received a subcutaneous injection of epinephrine in oil (1 mg. per kg.). Each animal served as its own control in an experiment carried out in the same manner with water substituted for the glucose solutions.

The effect of insulin alone on the epinephrine-induced hyperlipidemia was explored by injecting subcutaneously a mixure of from 2 to 3 units per kg. of crystalline insulin and from 1 to 1.5 units per kg. of long-acting insulin (NPH or Protamine Zinc insulin) at the same time as epinephrine in oil. In five out of eight experiments 50 g. of glucose was given by stomach tube 6 hours after the insulin injection, to prevent the development of hypoglycemia due to the long-acting insulin preparation. Each animal served as its own control, receiving the same dose of epinephrine without insulin.

Serum free fatty acids (FFA) were determined by a modification of the method of Gordon (9). Total lipids and triglycerides were determined by the method of Bragdon (10). Cholesterol was measured by the Sperry-Webb procedure (11), and lipid phosphorus by a modification of the procedure of Stewart and Hendry (12). Blood glucose was measured colorimetrically by the Somogyi-Nelson method (13).

Ultracentrifugal separation of serum lipoprotein fractions was performed according to the procedure of Havel *et al.* (14).

[2] Red Heart Dog Food, John Morrel and Co., containing 5.2 per cent total fat, as estimated from dichromate oxidation value (10).

[3] Dr. D. M. McCollester, personal communication.

TABLE 1. SERUM LIPID LEVELS (MG./100 ML.) DURING 24 HOURS FOLLOWING A SINGLE INJECTION OF LONG-ACTING EPINEPHRINE

Hours After Injection	Total Cholesterol				Free Cholesterol				Phospholipids				Triglycerides			
	Dog No. 1	Dog No. 4	Dog No. 6	Control	Dog No. 1	Dog No. 4	Dog No. 6	Control	Dog No. 1	Dog No. 4	Dog No. 6	Control	Dog No. 1	Dog No. 4	Dog No. 6	Control
0	143	125	117	130	38	37	33	32	342	299	266	296	29	75	42	31
3	149	123	115	126	36	36	32	33	370	329	258	283	68	29	35	44
6	151	134	129	132	41	39	36	33	360	299	291	284	45	65	47	30
24	165	173	155	133	46	60	47	35	418	444	384	316	70	67	48	55

RESULTS

Serum Lipid Changes in Dogs After a Single Dose of Epinephrine. Figure 1 presents the changes in FFA concentration during the first 24 hours following the injection of epinephrine in oil in three out of nine animals studied, and the mean curve. The three representative curves demonstrate the prompt increase in serum FFA which, however, did not persist throughout the period of observation. The FFA levels reached a peak of from two to three times the initial value within 1 to 3 hours, returning toward the normal range by 6 hours. In the control dogs injected with peanut oil, the gradual increase in serum FFA concentration during the experimental period may be attributed to continuous fasting (5). The somewhat higher levels at 24 hours in both control and experimental animals may be similarly explained.

In contrast to the response of serum FFA, little or no significant increase in the concentration of other lipids was observed at 6 hours. However, 24 hours after the injection highly significant increases in the levels of cholesterol and phospholipids had occurred (Tables 1 and 2). The changes in triglyceride levels were smaller and highly variable as is indicated by the large standard deviation.

In order to establish whether the response to epinephrine might be affected by the manner of administration of the hormone, a saline solution of epinephrine was infused into a fasting, anesthetized dog. As shown in Figure 2, it was not possible, even by constant intravenous infusion of increasing amounts of epinephrine, to sustain the initial increase in serum FFA. The response of the other lipids was similar to that obtained with the long-lasting epinephrine preparation.

Effect of Long-term Administration of Epinephrine in Oil. The effect on serum lipids of daily admin-

TABLE 2. SERUM LIPID CHANGES IN DOGS TREATED DAILY WITH EPINEPHRINE *

No. of Days of Epinephrine Treatment	No. of Animals	Per Cent Increase ± SD of the Initial Lipid Level				FC/TC	TC/PL
		TC	FC	PL	TG		
						mg./mg.	*mg./mg.*
0	19					.279	.435
1	19	28.6 ± 7.9	49.6 ± 18.7	41.0 ± 13.9	24.8 ± 34.4	.323 †	.397 †
3	7	60.1 ± 25.8	79.5 ± 34.6	48.2 ± 23.6	33.2 ± 13.3	.301 ‡	.489 ‡
6-8	6	90.9 ± 50.0	93.5 ± 60.2	52.7 ± 22.5	16.9 ± 49.0 §	.273 §	.549 ‡

TC = total cholesterol FC = free cholesterol PL = phospholipids TG = triglycerides

* All serum lipid elevations are significant relative to the zero time control levels with a p value less than 0.01, except for the triglyceride level at 6-8 days, which is not significantly different from that at zero time. The FC/TC and TC/PL ratios represent mean values averaged over all sera collected at the indicated times. In both sets of data significance was evaluated on paired data, each dog serving as his own control.

† Significantly different from zero time value at $p < 0.001$.

‡ Significantly different from zero time value at $p < 0.05$.

§ Not significantly different from zero time value.

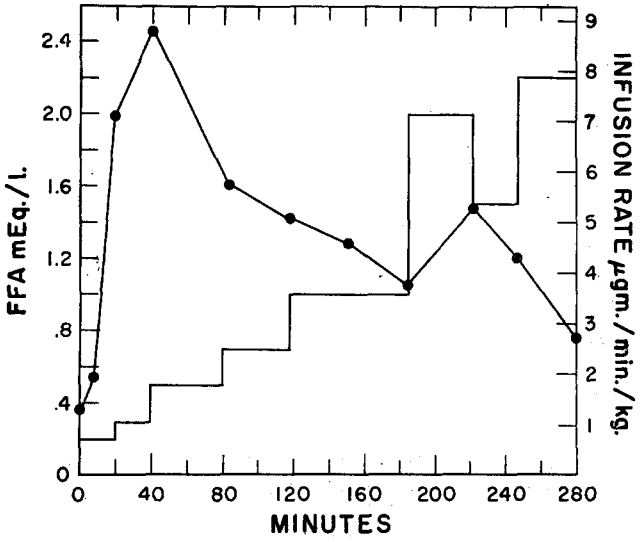

FIG. 2. Effect of continuous infusion of aqueous epinephrine on serum FFA levels. Twelve mg. of epinephrine in saline solution was infused into a Pentothal® anesthetized dog weighing 14 kg. The increasing rate of infusion is indicated by the steps in the figure.

istration of epinephrine in oil is represented in Figure 3 and Table 2.

The cholesterol and phospholipids, which became significantly elevated within 24 hours, remained at a high level as long as the animals continued to receive the hormone. It is of interest that the percentage rise of the free cholesterol fraction at 24 hours was considerably larger than that of esterified cholesterol, as is evidenced by the increased free to total cholesterol ratios. With continuation of epinephrine treatment, these ratios returned to normal.

The phospholipid elevation after one day of epinephrine treatment was proportionately greater than the rise in cholesterol resulting in lowered cholesterol to phospholipid ratios. The cholesterol level, however, continued to rise sharply, and after 6 to 8 days of treatment the cholesterol to phospholipid ratios became markedly increased when compared with the initial values.

The triglyceride levels have shown considerably more variability than those of the other serum lipids. This was true of the fasting control levels in various animals and also of the levels in the same animal at different times (Table 1). Furthermore, the triglyceride levels in treated animals fluctuated widely in contrast to the more sustained responses of the other lipids (Fig. 3). Whereas the cholesterol and phospholipid levels continued to rise with extended epinephrine treatment, the triglycerides did not. After 6 to 8 days they did not differ significantly from the zero time value.

When assessing the significance of the triglyceride changes, it should be stressed that in Tables 1 and 2 the changes are expressed as percentages of a component which is present in dog serum at low levels, and is determined by a method that depends upon calculation by difference (10).

Composition of Serum Lipoprotein Fractions in Dogs Maintained on Epinephrine. Results of ultracentrifugal separation of three main classes of lipoproteins from three dog sera are summarized in Table 3. The sera were obtained before and after 1 or 8 days of daily administration of epinephrine. The elevation in serum lipids caused by epinephrine was accounted for by rises in the d = 1.019 to 1.063 and 1.063 to 1.21 lipoproteins, the d < 1.019 fraction showing very little change.

The major change occurred in the d = 1.019 to 1.063 fraction, normally a very small component, where the percentage rise in total lipid content after 8 days of epinephrine treatment was 352, 700, and 220 per cent in the three animals studied. The percentage rise in the d = 1.063 to 1.21 fraction was considerably smaller (18, 15, and 41 per cent), but since this fraction is so much larger, the absolute increments, as shown in Table 3, nevertheless accounted for 39, 17, and 64 per cent of the total recovered lipid increment.

The elevation of the cholesterol to phospholipid ratio after 8 days of epinephrine treatment (Table 2) correlates with the marked elevation of the d = 1.019 to 1.063 fraction, in which this ratio is higher than it is in

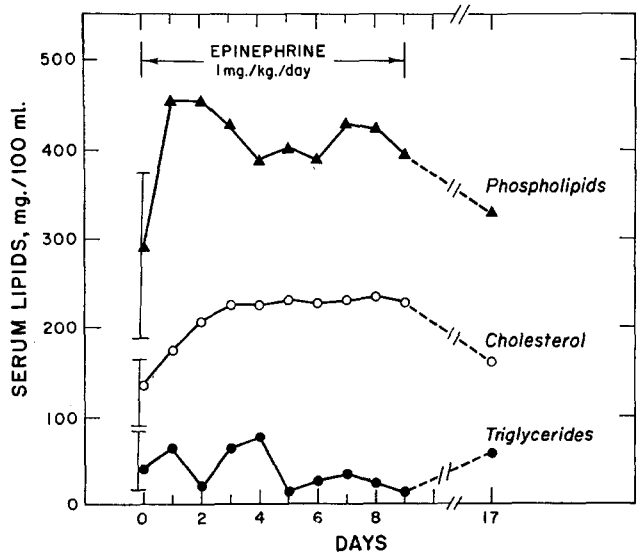

FIG. 3. Serum lipid response to prolonged administration of epinephrine in oil. Representative experiment in which a male dog weighing 14 kg. received subcutaneous injections of epinephrine in oil 1 mg./kg./day for 9 days. The vertical bars parallel to the ordinate indicate the range of normal fasting serum lipid values found in 19 dogs used in this study.

TABLE 3. COMPOSITION OF SERUM LIPOPROTEIN FRACTIONS IN DOGS TREATED WITH EPINEPHRINE

	mg./ 100 ml. of:	Dog No. 1			Dog No. 2			Dog No. 3				
		Control	Treated 8 Days	Net Change	Control	Treated 8 Days	Net Change	Control	Treated 1 Day	Net Change	Treated 8 Days	Net Change
Whole Serum	TL	633	910	*277*	546	995	*449*	547	820	*273*	811	*264*
	TC	155	231	*76*	126	277	*151*	130	176	*46*	214	*84*
	PL	364	518	*154*	296	487	*191*	283	481	*198*	449	*166*
	TG	41	54	*13*	65	98	*33*	69	83	*14*	43	*−26*
d < 1.019	TL	36	34	*−2*	63	59	*−4*	36	63	*27*	30	*−6*
	TC	4	4	*0*	3	8	*5*	5	7	*2*	4	*−1*
	PL	6	7	*1*	6	15	*9*	6	11	*5*	7	*1*
	TG	25	22	*−3*	53	34	*−19*	23	45	*22*	17	*−6*
d = 1.019-1.063	TL	35	193	*158*	50	400	*350*	45	101	*56*	144	*99*
	TC	8	53	*45*	14	114	*100*	11	27	*17*	43	*32*
	PL	16	85	*69*	23	180	*157*	15	46	*31*	57	*42*
	TG	10	35	*25*	9	65	*56*	14	15	*1*	18	*3*
d = 1.063-1.21	TL	567	669	*102*	426	491	*65*	422	592	*170*	595	*173*
	TC	144	165	*21*	103	128	*25*	104	133	*29*	157	*53*
	PL	341	406	*65*	260	292	*32*	236	377	*141*	345	*109*
	TG	10	15	*5*	10	4	*−6*	16	15	*−1*	18	*2*

TL = total lipids TC = total cholesterol PL = phospholipids TG = triglycerides

either of the other density classes. In addition, however, it is noteworthy that the lipid pattern within the density classes changed during epinephrine treatment. In both the d = 1.019 to 1.063 and the d = 1.063 to 1.21 classes the cholesterol to phospholipid ratio fell after 1 day of treatment and then returned to normal values after 8 days of treatment. These changes correlate with the significant drop in the ratio at 1 day recorded in Table 2.

Influence of Epinephrine on Serum Triglyceride Levels in Relation to Exogenous Fat Intake. It was necessary to evaluate any possible role of fat intake upon the hyperlipidemia induced by epinephrine, especially since epinephrine is known to decrease the motility of the gastrointestinal tract and possibly delay the processes of food absorption.

A single-dose high-fat meal was given to dogs and the serum lipid changes followed through 24 hours. The response of FFA, cholesterol, and phospholipids was similar to that in dogs fed a fat-poor diet. The duration of alimentary lipemia, however, was considerably prolonged by epinephrine (Fig. 4).

The Effect of Epinephrine on the Removal Rate of Blood Chylomicrons. The prolonged increase in triglyceride levels following epinephrine injection in the dog consuming large quantities of fat (Fig. 4) suggested that this might represent a retardation by epinephrine, either of the absorption of fat or of the removal of absorbed fat from the blood stream. Measurements of the disappearance time of intravenously injected chylomicrons were therefore undertaken. The curves shown in Figure 5 do not indicate any significant effect of epinephrine upon the half life of the circulating chylomicrons. It should be noted that the experimental methods here limit the accuracy of the determination of so short a half life. However, since the experiments were carried out in dogs serving as their own controls, each time being injected with comparable amounts of chylomicrons, and since the half-life values obtained were in no case prolonged by epinephrine, the conclusion that there is no significant retardation of chylomicron removal by epinephrine seems to be warranted.

Effect of Glucose Administration on the Epinephrine-induced Hyperlipidemia. It has been demonstrated previously that following a carbohydrate meal, plasma FFA concentrations are diminished and that the rate of release of FFA from adipose tissue *in vitro* is diminished by glucose (5, 6, 7). Experiments were performed to determine whether glucose given with epinephrine would inhibit the characteristic changes in FFA levels and whether any parallel

TABLE 4. EFFECT OF ADMINISTRATION OF GLUCOSE AND OF INSULIN ON THE EPINEPHRINE-INDUCED CHANGES IN SERUM LIPID LEVELS

	No. of Animals	Per Cent Elevation of Lipids *			
		TC	FC	PL	TG
Epinephrine only	3	30.7	44.5	43.0	12.5
Epinephrine + glucose		23.5	36.0	25.2	31.1
Epinephrine only	5	25.2	41.2	37.8	3.1
Epinephrine + insulin		16.8	28.5	23.0	2.9
Significance of difference between epinephrine and epinephrine + insulin-treated animals (paired data)		$p < 0.02$	$p < 0.01$	$p < 0.10$	not significant

TC = total cholesterol FC = free cholesterol PL = phospholipids TG = triglycerides

* Mean elevation measured 24 hours after injection of epinephrine in oil (1 mg/kg.).

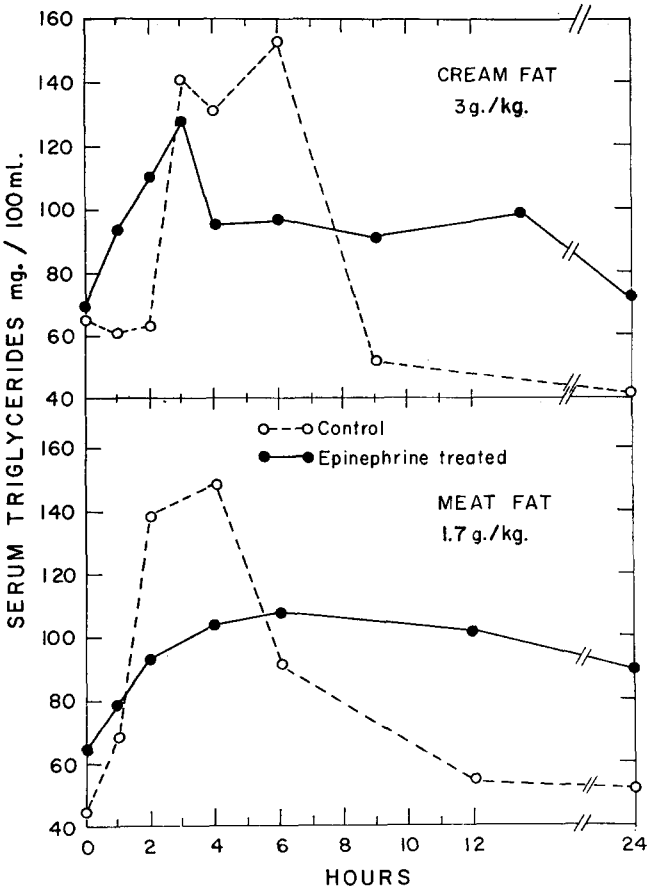

FIG. 4. Serum triglyceride levels in dogs after fat load. Representative experiments in 2 dogs receiving oral cream or meat fat loads with and without epinephrine in oil (1 mg./kg.).

effect would be observed on the epinephrine-induced changes in other serum lipids. Dogs receiving glucose by stomach tube were given a single injection of epinephrine in oil. It is seen from Figure 6 that in the control experiments in which epinephrine only was given, the peak FFA elevation occurred before the maximal epinephrine-induced hyperglycemia was reached. As the blood glucose rose, the FFA values returned toward normal. When glucose was administered to the same animal along with the epinephrine, the blood level of FFA dropped and then did not rise above normal (five experiments). On the other hand, as recorded in Table 4, feeding with glucose did not prevent the characteristic rise in cholesterol and phospholipids 24 hours after epinephrine, although there was some decrease in the magnitude of the response.

Effect of Insulin on Epinephrine-induced Hyperlipidemia. The demonstrated effect of glucose on the epinephrine-induced lipid mobilization prompted further attempts to modify the epinephrine response with insulin alone. It was of particular interest to explore whether the early elevation of blood glucose levels produced by glucose administration was essential for the effect on FFA described above.

As shown in Figure 7, insulin abolished the characteristic FFA response following epinephrine (eight experiments). At the same time the epinephrine-induced hyperglycemia was either completely prevented (five experiments) or sharply reduced (three experiments).

These results demonstrate that hyperglycemia per se is not essential to prevent the rise in FFA; the effects of glucose administration and the present results with insulin alone probably reflect increased utilization of carbohydrate.

The effect of insulin on epinephrine-induced changes in other serum lipids is shown in Table 4. It is noteworthy that although serum FFA elevation is blocked in the insulin-treated dogs, there is still a definite effect of epinephrine on serum cholesterol and phospholipids. The elevation in both lipids was, however, less marked when insulin and epinephrine were given as compared with the response of the same dogs treated with epinephrine only.

DISCUSSION

Two distinct lipid-mobilizing activities of epinephrine should be recognized. First, it stimulates the release of free fatty acids (FFA) from tissue depots; second, it causes an elevation of serum lipoprotein levels. It would be important to know whether these two responses are effected through a common primary mechanism of action. It is possible that the FFA responding rapidly to epinephrine may induce in turn the subsequent changes in serum lipoprotein levels. High blood levels of FFA could stimulate lipoprotein synthesis through incorporation of the fatty acid residues into the lipid moieties of the lipoproteins or, alternatively, the increase in circulating lipoproteins might represent a response to the need for an auxiliary FFA carrier protein in addition to albumin. There are a number of clinical situations in which there is an association of high blood levels of both FFA and lipoproteins, notably in uncontrolled diabetes mellitus and starvation (15). In the nephrotic syndrome, where serum albumin concentrations are much below normal, the lipoproteins are elevated and assume a much larger than normal share in blood FFA transport, as shown by Shafrir (16).

The results of the present study, however, suggest that the effects of epinephrine on lipoproteins may in fact not be strictly correlated with its effects on FFA levels. The rise in FFA after epinephrine is marked but short lived. It appears promptly but it cannot be sustained either by continuous infusion of large amounts of saline solutions of the hormone or by the administration of long-acting epinephrine in oil. The FFA level returns to normal before significant elevations in the cholesterol and phospholipid values are noticed. Furthermore, by raising the blood level of glucose prior to the injection of epinephrine or by enhancing glucose utilization by simultaneous insulin

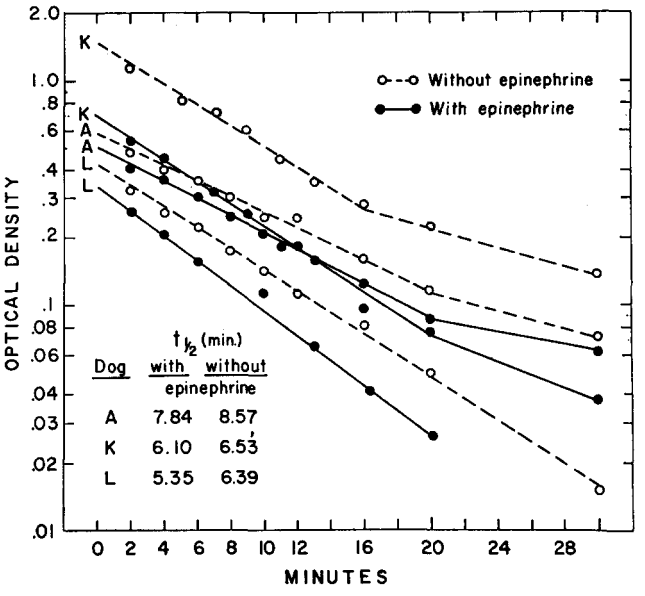

FIG. 5. Chylomicron disappearance curves in three dogs (K, A, and L) with and without prior administration of epinephrine. Epinephrine in oil (1 mg./kg.) was given subcutaneously 30 minutes prior to injection of chylomicrons. Dog K had been given the same dose of epinephrine daily for 2 days and received a third dose on the day of study. Half lives were calculated from the mean slope of the straight line portion of the curves during which more than 90% of the injected chylomicrons disappeared from the circulation

administration, the FFA level can be prevented from rising, and yet this does not prevent the characteristic elevation of cholesterol and phospholipids observed 24 hours after epinephrine. This dissociation of the two responses, however, must be further explored, in particular by studies of the turnovers of FFA and other blood lipids under these conditions.

From the time relationship of the peaks of the serum FFA and glucose curves in normal dogs receiving epinephrine (Figs. 6 and 7), it appears that as the blood glucose level rises, the FFA level falls toward normal. This decline of the FFA level probably is related causally to the increasing level of blood glucose rather than to an exhaustion of the epinephrine effect. Availability of glucose as a calorigenic substrate has been shown by Gordon and by Dole to be a controlling factor in the FFA output of the adipose tissue (17, 18). Moreover, it has been shown by Goldfien and Havel that the FFA response to norepinephrine, which does not produce marked hyperglycemia, is sustained much longer than it is after epinephrine (19).

The serum lipid increment in response to epinephrine appears in the cholesterol- and phospholipid-rich lipoproteins of the 1.019 to 1.063 and 1.063 to 1.21 density class. As noted in Table 3, the percentage rise in the

d = 1.019 to 1.063 fraction was considerably greater than that in the d = 1.063 to 1.21 fraction, a finding compatible with the changes in serum cholesterol to phospholipid ratios with time of epinephrine treatment. Not all these changes, however, can be accounted for on this basis. It appears that the lipid composition of the ultracentrifugal fractions changed significantly, more cholesterol being included in the 1.063 to 1.21 fraction. Further studies of the lipoproteins produced under the influence of epinephrine may be helpful in exploring the limits of variability in lipoprotein synthesis.

The rise in free to total cholesterol ratio at 24 hours may represent rapid cholesterol mobilization from the liver, normally rich in free cholesterol, and the return to the original ratio after 8 days of treatment would represent progressive esterification of this new cholesterol.

Epinephrine caused no rise in the triglyceride-rich d < 1.019 lipoprotein fraction in the present studies. Small or insignificant effects of epinephrine on fasting dog serum triglycerides have been observed when the triglycerides were determined by a direct method of

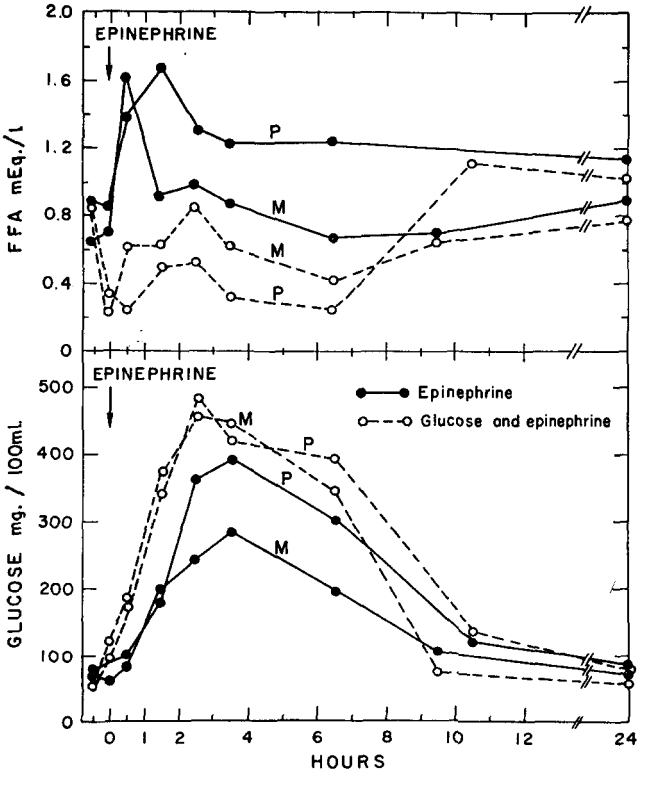

FIG. 6. Suppression of the FFA response to epinephrine by administration of glucose. Glucose solution was given intragastrically ½ hour before epinephrine and continued at ½ hour intervals as indicated in the Methods. In control experiments the same dogs received similar amounts of water along with epinephrine.

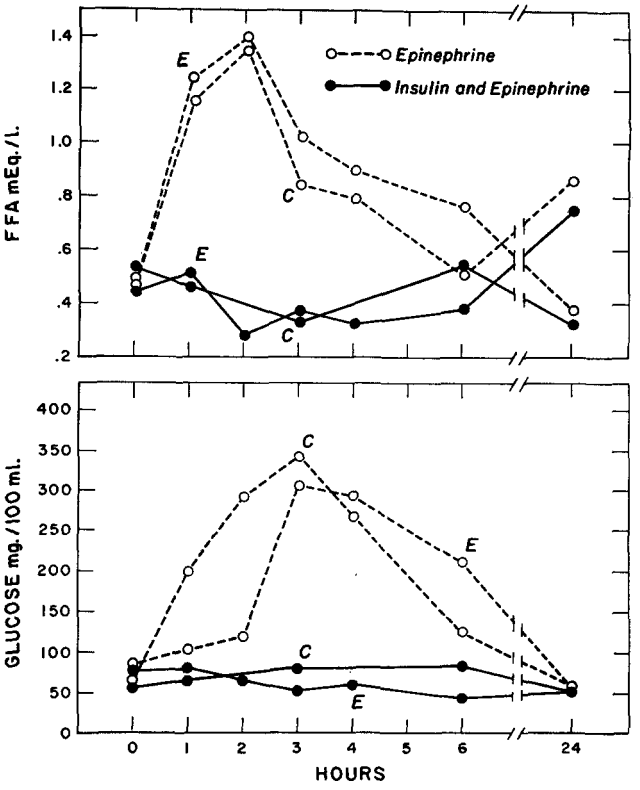

FIG. 7. Serum FFA and glucose levels following administration of insulin with epinephrine. Dogs C and E were injected with insulin and epinephrine at the same time (see Methods). In the control experiments they received epinephrine only.

Van Handel and Zilversmit (20).[4] Kaplan *et al.* (3) reported large percentage increases in dog serum triglyceride levels (70 to 100 per cent) following subcutaneous administration of epinephrine in oil. The changes in cholesterol and phospholipid levels were similar to those reported in this communication. It can be seen from Table 1 and Figure 1 that daily fluctuations in serum triglycerides of such an order of magnitude (expressed as percentage changes) are not uncommon and the technical difficulties in the determinations of triglyceride levels have been alluded to above. Moreover, the feeding schedule adopted by Kaplan *et al.* may be relevant since their epinephrine-injected dogs were fed canned meat during the experimental period. In view of the delaying effect of epinephrine on fat absorption described above, it may be possible that the 24-hour increase in the triglyceride levels noted by these investigators represented in part delayed fat absorption.

On the other hand, it appears that there may be a considerable species variation in the nature of the

[4] W. M. Butler, Jr., Dr. H. Maling, and Dr. B. B. Brodie, personal communication.

hyperlipidemia induced by epinephrine. Dury (4) reported a marked elevation in triglycerides and in low-density lipoproteins in fasting rabbits. But rats do not respond with elevation of triglycerides after long-lasting epinephrine (21). It is pertinent that rabbits, in contrast to dogs, respond with marked triglyceride elevations to treatment with cortisone or to the lack of thyroxine (22).

The possible relationship between the epinephrine-induced hyperlipidemia and the hypercholesterolemia reported by a number of investigators as an accompaniment of prolonged mental and emotional stress (23) and periods of tension (24) may be commented upon. Certainly these reactions entail adrenomedullary activity. Furthermore, the present results indicate that elevated cholesterol levels can be maintained over extended periods under the continuing stimulation of epinephrine. The possibility that the sympathetic nervous system triggers the lipid response directly by way of the adrenal medulla has to be considered along with the possibility of indirect stimulation by way of secondary release of specific pituitary lipid mobilizing factors. More recent studies in this laboratory have shown that both the FFA and the lipoprotein responses to epinephrine are abolished or markedly reduced in adrenalectomized or hypophysectomized rats (21) and dogs (22) and that normal responses to epinephrine are restored by treatment with cortisone. Thus it appears that increased secretion of both the medullary and the cortical hormones of the adrenal may be important in the hypercholesterolemia of the stress (25).

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