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Investigations with Regard to the Pathogenesis of So-called Fat Embolism *

Serum Lipids and Tissue Esterase Activity and the Frequency of So-called Fat Embolism in Soft Tissue Trauma and Fractures

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THE generally accepted view on fat embolism has, until quite recently, been that the emboli consist of mechanically released particles of fat, usually marrow fat from fractured bones. This fat is presumed to have been sucked into the veins and carried to the capillary system, where the fat particles lodged, thus causing hypoxia.

However, a considerable number of recorded observations definitely refute the correctness of this theory:

1. Fat emboli of a frequency so high as to be fatal are recorded in a large number of cases without traumatic injuries to bones or soft tissues. This occurs, for example, in cases of infection and various conditions of poisoning as well as superficial burns. Lehman and Moore [8] and Pearsall and Weaver [9] have given a survey of the abundant literature on this subject.

2. A discrepancy exists between the extent of the trauma and the frequency of fat embolism. Serious bone injuries can occur without fat embolism, while relatively slight fractures with small marrow lesions may lead to fatal fat embolism. Of interest in this connection is the fact that extensive injuries of the marrow in connection with Küntscher nailing of fractures do not cause increased frequency of fat embolism. This has been established by Böhler and Böhler [3] in 1949 and Street [14] in 1951 and others.

3. The spread of fat emboli occurs a remarkably long time after the trauma. Fat embolism may occur in close connection with the injury, but the frequency reaches its peak between the fourth and eleventh day after the trauma (Speed; [13] Scuderi,[12] a.o.).

If the fat embolism actually is caused by marrow fat getting into the injured veins at the fracture, it would be reasonable to assume that the frequency would be highest immediately after the injury, as a progressive thrombosis of the injured veins soon takes place together with coagulation of the hematoma.

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TABLE I. *Change in Serum Lipid Concentration*

Animals with Crushed Legs				Animals with Ligated Legs			
No.	Total Lipid	Cholesterol	Lipid-P	No.	Total Lipid	Cholesterol	Lipid-P
1.	+ 100	+ 3	+1,7	18.	+ 540	+ 46	+3,5
2.	+ 330	0	0	19.	+ 840		
3.	+ 110	+ 40	+2,5	20.	+2020	+153	
4.	+1140	+ 44	+9,8	21.	+ 290	+ 27	+1,6
5.	+1240	+142	+8,2	22.	+ 870	+ 45	+4,2
6.	+ 530	+ 6	+1,2	23.	+ 910		
7.	+1030	+ 35	+7,5	24.	+ 970	+ 70	+4,2
8.	− 20	+ 35	+0,8	25.	+ 80		
9.	+ 320	+ 40	+2,2	26.	− 30	+ 15	
10.	+ 960	+ 73	+3,7	27.	+ 630	+ 33	+1,4
11.	+1080	+ 87	+5,1	101.	+ 800	+ 32	+3,7
12.	+ 730	+ 62	+4,4	102.	+ 600	+ 29	+3,1
13.	+ 810	+ 64	+3,4	103.	+ 900	+110	+9,3
14.	0	+ 11	0	104.	+ 150	+ 21	—
15.	+ 130	+ 9	−1,2	105.	+ 960	+ 60	+6,8
				106.	+ 200	+ 24	+2,0
				107.	+1260	+ 74	+8,3
				108.	+ 300	+ 56	+4,3

4. Occurrence of fat emboli in capillary systems distal to the lungs. Fat embolism occurs not only in the lungs but also in the brain and abdominal organs such as, for instance, the kidneys. Doubt has repeatedly been expressed in the literature as to the possibility of loosened marrow fat being able to pass through the capillaries of the lungs and then lodging in another capillary system of much the same capillary width. This objection is in all probability valid. A reservation has to be made, however, for the possibility that a small portion of the pulmonary capillaries may have two or three times the width of, for example, the capillaries of the brain (Printzmetal *et al.*;[10] Tobin[19]). The practical significance of this small portion of wider capillaries is, however, doubtful in this connection.

5. High frequency of so-called fat emboli in ordinary postmortem material. Of essential interest in this connection is the fact that during microscopical examinations changes identical with those generally regarded as pathognomic of so-called fat embolism can be widely observed in "ordinary," i.e. not traumatic postmortem material. In 1928 Lehman and McNattin[7] discovered this picture in 50 per cent of the ordinary postmortem material of a hospital, and in 1932 Wright[21] found it in 52 per cent. As early as 1898 Carrara[4] showed that the picture of fat embolism could be established in 22 per cent of deaths caused by cardio-vascular diseases and in 44 per cent of deaths caused by burns. In 1920 Catzara[5] found the same picture in 18 of 67 cases of pneumonia.

It is interesting to compare the frequency of fat embolism after severe bone injuries. Robb-Smith[11] examined 125 who had died after suffering shrapnel injuries in World War II, and observed fat embolism in the lungs in 41 cases. Twelve of these had no observable bone injuries, but the cause of death was still believed to be the so-called fat embolism. Krücke[6] discovered fat embolism in the lungs in only 31 per cent of the corpses of injured airmen. Wakely[20] found fat embolism in 40 per cent of fatally burned cases in 1941.

It thus seems as though the microscopic picture we regard as characteristic of so-called fat embolism were as common in the ordinary postmortem material of a hospital as in material based on cases of severe injuries.

The question thus arises as to the existence of emboli of fat torn loose in cases of bone and soft tissue traumata. It seems more likely that the fat emboli develop in the capillaries of the organs—that they are symptoms, either of a disturbance in the local lipid metabolism or a change of the state of emulsification of the neutral fat in serum, and that these disturbances are the secondary effects of tissue injuries.

In this work we shall begin by throwing light on the following points:

I. Can a quantitative change of the serum lipids be observed in injured animals with so-called fat emboli?

II. Is the frequency of fat embolism higher in cases of fractures than in those of only soft tissue injuries?

METHODS

Male rabbits weighing 2 to 3 Kg. were used. In 15 animals one hind leg (bone and muscle) was crushed by means of a blunt instrument without perforation of the skin. This was done to animals nos. 1 to 8 inclusive under pentothal narcosis lasting 5 to 15 minutes and to animals nos. 9 to 15 inclusive under 5 to 15 minutes ether narcosis.

On 17 other animals the hind leg was ligated for 60 to 120 minutes, i.e. so long that small hemorrhages and edema developed in the tissue due to venous stasis. This ligation was carried out under spinal anesthesia by means of xylocaine hydrochloride.

Prior to the experiment 15 ml. of blood was taken for analysis by cardiac puncture. The animals were put to death 12 to 36 hours after the injury through blood letting by cardiac puncture.

Serum Lipid Analyses. Serum was dripped into pure alcohol heated to just below boiling point. Further extraction of fat from the precipitate was carried out in a Soxhlet apparatus with pure alcohol for five hours. After careful evaporation of the extraction medium the lipids were redissolved in chloroform. From several portions of this chloroform solution determinations were made of:

Total lipids by means of evaporation and weighing of the residue, *Cholesterol* according to the method of Theorell and Widström,[18] and *Lipidphosphorus* after evaporation of the chloroform, digestion of the residue with 30 per cent sulphuric acid, redissolved in water, and phosphate determination according to the method of Briggs.[2] Serum lipid concentrations were expressed in milligrams per 100 ml.

Esterase activity was determined in tissue suspensions according to a previously described method using tributyrine (Svanborg[15]) and Tween 20 (Svanborg[16]) as substrates. Esterase activity was expressed in ml. 0,05 n-KOH per gram dry weight of tissue.

Investigation of the Occurrence of "Fat Embolism." Within five minutes after the death of the animal, pieces of tissue were fixed in a 10 per cent solution of formaldehyde, sectioned and stained with Sudan III.

RESULTS

Ad I: Concentrations of serum lipids were investigated before and after the injury of 15 rabbits with crushed legs and 17 rabbits with ligated legs.

As we can see from Table I an increase of the lipid contents in serum, in many cases a considerable one, developed in most of the animals during the 12 to 36 hours the experiment lasted. This increase, quantitatively equal in animals with crushed legs and ligated legs, comprized in equal proportions cholesterol, phosphor lipids and total fat. Previous determinations had shown that starvation of short duration or blood letting in quantities needed for these analyses, could not in themselves explain this increase of serum lipids (Svanborg[15]). The lipid increase was the same, no matter whether spinal anesthesia, pentothal or ether narcosis was used. There have been no previous observations to indicate that pentothal narcosis or spinal anesthesia should have affected the content of serum

TABLE II. *Esterase Activity*

Animals with Crushed Legs					Animals with Ligated Legs		
	Kidney		Liver			Kidney	Liver
No.	Tween 20	Tributyrin	Tween 20	Tributyrin	No.	Tween 20	Tween 20
1.	130	290	250	480	18.	130	250
2.	100	260	200	400	19.	140	280
3.	110	310	170	400	20.	150	300
4.	110	230	210	680	21.	170	280
5.	180	180	230	350	22.	160	220
6.	160	820	280	980	23.	180	250
7.	120	440	250	610	24.	180	310
8.	110	400	240	680	25.	150	270
9.	120	570	220	760	26.	140	270
10.	90	550	220	740	27.	220	260
11.	140	530	230	580		—	—
12.	130	480	330	940	M	162	269
13.	110	500	250	620	s	26	27
14.	100	390	190	530			
15.	130	400	230	640			
16.	140	280	270	580			
17.	120	480	280	800			
	—	—	—	—			
Mean	124	418	238	634			
Standard deviation	23	157	30	176			

lipid. Svanborg showed in 1951 that pentothal narcosis of the same duration and depth as used in these experiments does not affect the serum content of lipid in the rabbit.

It must therefore be considered established that the increase in serum lipid observed has been released by the injuries.

The cause of this increase in serum lipid must be either delayed decomposition of the fat, increased fat synthesis, or intensified mobilization of fat from depots.

To find whether delayed decomposition of fat occurred in these injured animals, the esterase activity in tissue suspensions from kidney and liver was determined (Table II) and compared with the esterase activity in normal animals (Table III). A comparison of these results is given in Table IV together with the results of determinations of esterase activity in animals exclusively treated with ether narcosis. The reason for this investigation will be discussed below.

As appears from the tables, no definite change in the esterase activity could be observed in the injured animals.

Ad II: The frequency of fat embolism in cases of marrow injuries only as compared with soft tissue injuries only.

Table V shows the results of the experiments with the animals in which, simulta-

TABLE III. *Normal Animals. Esterase Activity*

	Kidney		Liver	
	Tween 20	Tributyrin	Tween 20	Tributyrin
	150	480	190	540
	120	330	220	430
	160	470	270	640
	150	450	270	690
	230	520	250	690
	230	460	260	560
	150	420	260	450
	100	320	260	470
	120	410	220	800
	100	530	200	600
	110	260	220	460
	200	580	270	680
	160		250	
	200		260	
	150		230	
	—	—	—	—
Mean	155	436	242	584
Standard deviation	42	93	32	118

TABLE IV. *Esterase Activity*

	Kidney		Liver	
	Tween 20	Tributyrin	Tween 20	Tributyrin
Normal animals	155 ± 11	436 ± 27	242 ± 8	584 ± 34
Animals with crushed legs	124 ± 6	418 ± 38	238 ± 7	634 ± 42
Animals with ligated legs	162 ± 8		269 ± 9	
Animals after ether anesthesia	127 ± 9	445 ± 17	238 ± 11	607 ± 38

TABLE V. *Fat Embolism and Change in Serum Lipid Concentration*

	Change in Serum Lipid Concentration			Fat Embolism			
No.	Total Lipids	Cholesterol	Lipid Phosphorus	Lung	Liver	Kidney	
5.	+1240	+142	+8,2	+	−	++	Crushed
6.	+ 530	+ 6	+1,2	+	−	(+)	legs
7.	+1030	+ 35	+7,5	+	−	(+)	
8.	− 20	+ 35	+0,8	++	−	−	
9.	+ 320	+ 40	+2,2	(+)	−	−	
10.	+ 960	+ 73	+3,7	−	−	−	
11.	+1080	+ 87	+5,1	(+)	−	(+)	
12.	+ 730	+ 62	+4,4	(+)	−	(+)	
13.	+ 810	+ 64	+3,4	+	−	(+)	
14.	0	+ 11	0	−	−	−	
15.	+ 130	+ 9	−1,2	(+)	−	−	
101.	+ 800	+ 32	+3,7	(+)	−	−	Ligated
102.	+ 600	+ 29	+3,1	+++	−	+	legs
103.	+ 900	+110	+9,3	++	−	+	
104.	+ 150	+ 21	—	+	−	−	
105.	+ 960	+ 60	+6,8	+	−	−	
106.	+ 200	+ 24	+2,0	(+)	−	−	
107.	+1260	+ 74	+8,3	+++	−	+	
108.	+ 300	+ 56	+4,3	++	−	+	

+++ = Abundant fat emboli in all fields of vision.
++ = Some fat emboli in all fields of vision.
+ = Fat emboli in single fields of vision.

neously, the changes in serum lipid and the frequency of fat embolism were studied. It shows that *the frequency of fat embolism was as high in injured animals without fractures as in those with extensive ones, and also that this frequency was not definitely proportionate to the quantitative change of the serum lipids.*

A number of authors have shown the increase in serum lipids after ether or chloroform narcosis of long duration. It has been believed that this increase in lipid has been initiated by the anesthetics, because it has not been observed in connection with narcosis caused by other means, such as, for example, barbiturates (Adriani [1]). As pointed out above, the anesthetics used in this investigation did not affect the increase in serum lipid or the frequency of fat embolism. Determinations after 30 minutes of ether narcosis in ten healthy rabbits also showed that the increase in concentration of serum lipid started by the narcosis occurred later than that after trauma, and that this increase in lipids after 30 minutes ether narcosis only occurred in about half of the animals (see Fig. 1). At the end of the test the animals were killed and determinations of esterase activity made in suspensions from the kidney and liver (Table VI). The esterase ac-

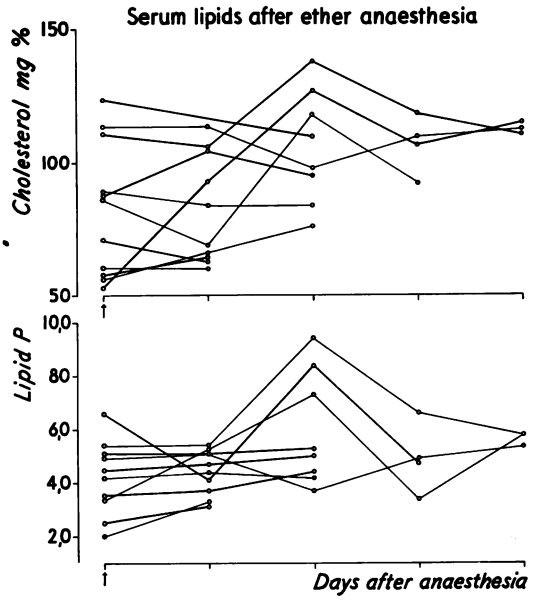

FIG. 1.

tivity did not differ from that of the normal animals (Table IV).

COMMENTS

The results showed that accumulations of droplets of fat in the tissue capillaries, and of the type commonly considered pathognomonic of so-called fat embolism, occur as frequently in connection with injuries to soft tissue as in cases of fractures with injuries of the marrow. No blood stasis, thrombosis, etc. could be observed in conjunction with the so-called fat emboli. This definitely refutes the previous theory that the so-called fat embolism consists of marrow fat torn loose and drawn into the circulation.

The increase in the content of lipid of the serum after trauma shows that a disturbance of fat metabolism occurs in these injured animals. The cause of this disturbance is uncertain. The fact that there is no decrease of esterase activity in hepatic and renal tissue in vitro refutes the assumption that the increase in serum lipid is due to reduced decomposition of the lipids. This question is, of course, not finally solved through the mere study of esterase activity in vitro.

TABLE VI. *Animals After Ether Anesthesia. Esterase Activity*

No.	Kidney		Liver	
	Tween 20	Tributyrin	Tween 20	Tributyrin
28.	100	490	240	520
29.	120	400	280	650
30.	120	430	230	630
31.	160	490	250	740
32.	120	460	200	480
33.	140	400	230	620
Mean	127	445	238	607
Standard deviation	21	41	26	94

These results and the clinical experiences quoted in the introduction raise the question as to the existence of embolism by traumatically released fat. No accumulation of fat occurred in the larger arteries of the injured animals. It seems more likely that the occurrence of droplets of fat in blood vessels after trauma, for example, is a symptom of a local disturbance of the emulsification of the serum lipids, or a change of the serum lipids with an increase of lipids colorable with Sudan.

In these experiments the frequency of fat emboli did not occur in a definite proportion to the serum content of lipid. Clinical evidence, supporting the view that fat embolism should be more common among individuals with diseases accompanied by hyperlipemia, does not exist. It seems likely, therefore, that quantitative changes in serum lipid play a lesser part than qualitative. Svanborg and Svennerholm [17] in 1955 made a more thorough analysis of the serum lipid in a patient who died of so-called fat embolism after fractures. The analysis did not reveal any quantitative deviations from the normal. This supports the view that so-called fat embolism is a symptom of a local change in emulsification of the serum lipids in the capillary system of parenchymatous organs, or a change in the serum lipids connected with an increase of lipids colorable with Sudan. It seems likely that the occurrence of these fatty

droplets is *one* change in a complex of symptoms comprising shock, tissue injuries and a change of the emulsification of the serum lipids. It is not certain that the occurrence in the capillaries of fat colorable with Sudan is of any clinical importance.

SUMMARY

A survey of the literature on the clinical experience with so-called fat embolism shows, with a high degree of probability, that the emboli do not consist of marrow fat torn loose through injury.

Experiments with rabbits, some of them injured through crushing and some by ligating their hind legs, have been reported. After the injury, fat colorable with Sudan could be observed in tissue capillaries. Fat of the type commonly considered pathognomonic of so-called fat embolism was found to occur as frequently after soft tissue injuries as in cases of fractures.

Within a period of 48 hours after trauma an increase of total fat, cholesterol and phosphor lipids occurred in the serum.

A 30-minute ether narcosis was found to start a less pronounced increase in serum lipid, occurring later.

Injury or ether narcosis does not cause changes in the esterase activity in vitro of hepatic or renal tissue. This refutes the assumption that the increase in serum lipid after trauma is due to reduced decomposition of lipids.

The frequency of fat embolism is not proportionate to the *quantity* of lipids in the serum. So-called fat embolism, i.e. the occurrence in the capillaries of parenchymatous organs of lipids colorable with Sudan, is probably a symptom of a qualitative change of the serum lipids. It cannot be considered definitely established that the occurrence in the organ capillaries of fat colorable with Sudan is of any clinical importance.

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