The syndrome of fat embolism and its origin

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The solution of the now century-old riddle of fat embolism has been much delayed by a misunderstanding which is reflected even in terminology.

In patients who die shortly after injury microscopic droplets of fat are found obstructing small vessels, particularly in the lungs but also sometimes in other organs. Lung embolism is found in nearly all patients when injury includes a fracture of a long bone. On the other hand, a well defined clinical syndrome is observed only in certain patients with bone fractures. The syndrome is characterized by severe pulmonary, circulatory, and neurological signs and symptoms which lead to death in a high percentage of cases. A distinction must be made between the pathological entity of fat emboli in small vessels of those who die after bone injury and the clinical syndrome. The relationship between the two phenomena is far from clear. As a consequence many surgeons believe that fat embolism is infrequent, whilst most pathologists find necropsy evidence of fat embolism to be very common. This confusion is mirrored in the statistics on

fat embolism where, depending on the criteria of diagnosis, its frequency is said to range between 5% and nearly 100% (Evarts, 1965). A study of the incidence and severity of fat embolism at necropsy among injured and uninjured cases was therefore undertaken.

Fat Embolism at Necropsy

The grading of fat emboli proposed by Sevitt (1962) was adopted. One hundred posttraumatic and 100 non-traumatic cases were studied. Forty-one of the injured patients with fractures died within a week of the accident: fat emboli were found in the lungs in every case, the average number of emboli being $1,017 \pm 259$ per mm^3 (Table I). After trauma fat droplets are reported to disappear fairly quickly from the lungs (Vance, 1931; Whiteley, 1954; Sevitt, 1960), and this was confirmed in the 33 patients with fractures who died one week or later after injury: in them the lung emboli count was only 89 ± 24 per mm^3 . In those without bone injury who succumbed to trauma within one week the lung embolus count was surprisingly high, 213 ± 117

Emboli per mm^3 Lung Section	Patients with Long Bone Fracture		Patients without Fracture		All Cases
	Death within One Week	Death after One Week	Death within One Week	Death after One Week	
0	0	4	1	6	11
0-60	6	16	5	5	32
60-180	3	9	5	0	17
Over 180	25	4	4	0	33
Over 1,800	7				7
Totals	41	33	15	11	100
Mean number of emboli	$1,017 \pm 259$	89 ± 24	213 ± 117	10 ± 6	

Table I Lung embolism in 100 patients dying after injury

Emboli per mm^3 Lung Section	Chronic Diseases	Acute Diseases	Totals
0	28	16	44
0-60	33	11	44
60-180	4	3	7
over 180	5	0	5
Totals	70	30	100
Mean number of emboli/ mm^3	37 ± 11.5	14 ± 4	

Table II Pulmonary fat embolism in 100 non-traumatic necropsies

per mm^3 . In medical cases (Table II) the embolus counts were uniformly low, with a mean value of only 37 ± 11 emboli per mm^3 of lung in the 70 patients who died after a chronic illness and less in those with acute diseases. However, fat emboli were present in about half the medical cases and was more than slight in 13% (Tables I and II).

Gross lung embolism was found in 78% of those who died within a week of fracture, and in 17% the embolism was only considerable, with more than 1,800 emboli per mm^3 of lung.

Cerebral fat emboli were seen in over one-third of the cases and renal emboli in 50%. The correlation between the severity of pulmonary embolism and the presence of systemic emboli was confirmed. Those with cerebral embolism had $1,607 \pm 748$ emboli per mm^3 in the lungs as against a count of 744 ± 191 in patients without cerebral embolism.

It was hoped that some insight could be gained on the importance of these findings in the light of the experimental observations.

Experimental Embolism

Fat embolism was produced in rabbits by the injection of triolein. Mortality rates were studied

in relation to the dose injected, the route of administration, and other factors. Pulmonary and systemic fat embolism was studied by the same semiquantitative method as in the human cases. The distribution of the fat according to dose was also investigated in other groups of animals with ^{131}I -labelled triolein.

The minimal lethal dose (MLD) of intravenously injected triolein was found to be 1.50 ml/kg body weight, and the LD_{50} was 1.02 ± 0.022 ml/kg. Similar results were reported by Peltier (1956). These doses produced a very severe histological degree of fat embolism in the lungs. Even after 0.5 ml/kg lung emboli counts were over 12,000 per mm^3 . Cerebral emboli were found even with the smallest dose given: they were seen in three of the six rabbits receiving 0.1 ml/kg, and in nine of the 12 receiving 0.25 ml/kg triolein. All animals injected with larger doses had gross cerebral fat embolism. A linear increase of the injected dose increased the histological severity of cerebral fat embolism in an exponential manner: thus, 6 ± 2.4 emboli per mm^3 were found in brain tissue after the injection of 0.1 ml/kg and 284 ± 55 after 1.0 ml/kg of triolein. A similar relationship was found for several embolisms (Figs. 1 and 2).

After the injection of radioactive triolein the bulk of the injected oil was recovered from the lungs: after a dose of 0.1 ml/kg $75.5 \pm 5\%$ of

Fig. 1 Number of cerebral fat emboli. Continuous line: rabbits killed 2 hr after fat injections. Interrupted line: animals killed after 24 hr. Abscissa: number of emboli. Ordinate: dose of injected triolein.

Fig. 2 Number of renal fat emboli (key as in Fig. 1).

Fig. 3 Radioactive fat content of the lungs after intravenous administration of ^{131}I -triolein. Continuous line: percentage of injected dose. Interrupted line: μl per gram fresh tissue.

the fat was found in the lungs. The percentage pulmonary recovery decreased as the dose increased, and a greater part of the injected fat gained access to the systemic circulation and ultimately produced fat embolism in other organs. Thus, the renal uptake of labelled oil after a dose of 0.1 ml per kg was 0.37%, and it increased to 1.23% after 1.0 ml/kg was given, whilst the hepatic uptake rose from 0.82 to 10.4% with these dosages. The same phenomenon was observed in the brain; with a ten-fold increase of dose there was a hundred-fold increase in the amount of fat recovered from brain tissue (Fig. 3).

Comparing our necropsy observations in man with the results of the rabbit experiments, it was interesting to note that the pulmonary embolus counts in the most severe cases, more than 1,800 emboli per mm^3 , observed in 17% of patients dying within a week of fracture, are approximately equal to those in the rabbits receiving an intravenous injection of 0.1 ml/kg triolein. These results, which are in accord with those of Armin and Grant (1951), indicate that the minimal lethal dose of neutral fat in the experimental animal is more than 10 times greater than the quantity of that which has probably entered the circulation in the most severe human cases (Fig. 4).

There is, however, a very important difference between clinical and experimental fat embolism. After the injection of a lethal dose of fat symptoms appear almost immediately and the animal dies within a few hours in utter respiratory distress.

On the other hand, in man the clinical syndrome

appears after a latent period, the first symptoms developing only on the second or third day after injury: pulmonary symptoms, dyspnoea, and slight cyanosis may be present, but in the more severe cases the clinical picture is dominated by cerebral symptoms. In the light of these very impressive symptoms, the opinion has been repeatedly expressed that the syndrome is produced by systemic, especially cerebral, embolism, and that death occurs through involvement of the brain (Scriba, 1880; Grondahl, 1911; Armin and Grant, 1951; Sevvitt, 1962).

INTRAARTERIAL INJECTION OF FAT

If death from fat embolism is a sequel of systemic embolism, the mortality must depend on the amount of fat passing the lungs and reaching the arterial side of the circulation. To test this hypothesis, rabbits were given 0.25–1.5 ml/kg of triolein through a catheter introduced either into the left ventricle or simultaneously into both carotid arteries. Animals surviving were killed 72 hours after the injection for histological examination. The distribution of the fat was also studied with ^{131}I -labelled triolein.

The results seem important. First, the injection of fat directly into the arterial circulation did not increase the mortality significantly (Fig. 5). Secondly, the distribution of the fat was not much affected by the site of injection and by far the heaviest embolism was always found in the lungs. For instance, after injecting 0.50 ml/kg triolein into the carotid arteries, $6,640 \pm 1,484$ emboli per mm^3 were found in the lungs and only 22.6 ± 8.3 emboli in the brain. These observations were supported by the results of the experiments with radioactive triolein. Two hours after the intravenous injection of 0.50 ml/kg ^{131}I -triolein, $68.2 \pm 6.9\%$ of the dose was recovered from the lungs, and after injection into the left ventricle pulmonary recovery was 54.4%. The amounts found in other organs after the ventricular introduction did not differ significantly from those observed after intravenous injection. Similarly in dogs, a predominantly pulmonary accumulation of the labelled fat after an injection into the carotid artery was reported by Cobb, LeQuire, Gray, and Hillman (1958). These observations seem to disprove the primary importance of systemic embolization or at least the significance of the amount of fat passing through the pulmonary filter (Figs. 6, 7, and 8).

PULMONARY FAT EMBOLISM AND HYPOXIA

The functioning of the lungs as a filter of unemulsified fat was investigated in a further series of experiments. The left main pulmonary artery was ligated and triolein in doses ranging from 0.25 to 1.25 ml/kg was injected intravenously. Exclusion of the left lung from the circulation exerted little influence on the mortality from

Fig. 4 Amount of labelled fat in the individual organs after intravenous administration of ¹³¹I-triolein.

Fig. 5 Mortality of rabbits after intravenous fat injection. Groups of six animals each; ----- intravenous injection ————— injection into the left ventricle; injection into both carotid arteries.

Fig. 6 Pulmonary embolus counts following triolein injections ----- intravenous injection ————— injection into the left ventricle, injection into both carotid arteries.

Fig. 7 Cerebral embolus counts in rabbits following triolein injections (key as in Figure 6).

Fig. 8 Renal embolus counts following triolein administration ————— intravenous injection
----- injection into both carotids.

experimental fat embolism. Further, embolus counts in the right (intact) lungs after various doses of triolein were at least as high as in the lungs of the control animals. Experiments with radioactive oil showed that after the injection of 0.25 ml/kg triolein $74.5 \pm 3.5\%$ of the amount injected was taken up by the intact right lung compared with a recovery of $74.9 \pm 8.5\%$ from both lungs in control animals without artery ligation (Fig. 9).

Further, with similar doses of fat embolus counts in the brain and kidneys of animals with unilateral lung artery occlusion were not significantly different from those found in control animals. The same can be said about the uptake of radioactive oil in various organs. Therefore reduction of the pulmonary vascular tree by about 45% did not significantly influence the efficiency of the lungs as a filter to fat droplets.

In the clinical syndrome of fat embolism, the lungs are not only functioning as a filter of the fat, but secondary changes in lung tissue are also present.

These changes are radiologically characterized by 'disseminated patchiness', a 'snowstorm appearance' of the lung fields (Maruyama and Little, 1962; Sevitt, 1962; Trautmann and Wetzel, 1962). Indeed there is a widespread infiltration, and the radiological picture is caused by perivascular and intraalveolar haemorrhage and oedema alternating with zones of emphysema (Robb-Smith, 1941). A decrease of arterial O_2 saturation is to be expected from these changes similar to that produced by other processes reducing alveolar gas exchange. Severe oxygen desaturation of the arterial blood has been reported in clinical cases of fat embolism (Sproule, Brady, and Gilbert, 1964; Collins, Hudson, Hamacher, Rokous, Williams, and Hardaway, 1968; Wertzberger and Peltier, 1968). In four patients observed by our group arterial oxygen saturation was less than 60% at the onset of the symptoms (Nagy, Serényi, and Szabó, in press). In one case, symptoms appeared without an appreciable latent period. The patient, an

Fig. 9 Lethal effect in fat embolism (dose effect curves). Groups of six rabbits each; ————— normal animals; ligation of left pulmonary artery; - - - - - left side pneumothorax.

80-year-old woman, had, however, severe senile emphysema, a thick callus on the pleura, and other signs of a chronic tuberculous process. In her, the absence of a latent interval seemed due to preexisting pulmonary disease which restricted alveolar gas exchange. The effect of the reduction of pulmonary ventilation on experimental fat embolism was therefore investigated.

In rabbits an open pneumothorax was produced on the left side. After the stabilization of the state of the animals, various doses of triolein were injected into the ear vein or through a catheter in the left ventricle. The distribution of the introduced oil was also studied with ^{131}I -labelled triolein.

The pneumothorax alone reduced arterial oxygen saturation from $91 \pm 1.2\%$ to $70.5 \pm 3.0\%$. The blood flow through the left lung after pneumothorax was $41.9 \pm 3.4\%$ of total pulmonary flow. The intravenous injection of 0.25 ml/kg triolein produced a further and marked reduction in arterial oxygen saturation, in most animals to below 20% . In a control group

of anaesthetized rabbits the intravenous injection of 0.25 ml/kg triolein alone reduced arterial oxygen saturation to $85 \pm 3.9\%$ only. When unilateral pneumothorax was produced 24 hours after the injection of oil the arterial O_2 saturation fell to $44 \pm 8.7\%$. However, unilateral pneumothorax reduced the lethal dose of fat dramatically with intravenous injection of triolein the LD $_{50}$ was 0.17 ml/kg and the MLD was 0.25 ml/kg .

Lung emboli counts and the pulmonary uptake of radioactive triolein after intravenous injection were generally lower on the side of the pneumothorax than in the intact right lungs or in the lungs of control animals. Total uptake by both lungs after the injection of 0.50 ml/kg of ^{131}I -triolein was 64.4% of the injected dose (Fig. 10) (Szabó, Magyar, and Jankovics, 1969a).

In animals with unilateral pneumothorax embolus counts in the kidneys, and especially in the brain, showed a marked increase. However, the most severe cerebral embolism was observed in the hypoxic animals who received the oil via the left ventricle. At the 0.50 ml/kg dose level the cerebral embolus count was $3,208 \pm 1,078$ per mm^3 (Szabó, Magyar, Jankovics, and Farkas, 1969b); when hypoxia was produced some time after the injection of fat, cerebral fat embolism was, however, not more severe than in non-hypoxic animals. On the other hand, if rabbits with a left-sided pneumothorax and receiving double the lethal dose of triolein for hypoxaemic animals, were placed immediately after the injection in an atmosphere of 100% oxygen, none of them succumbed to fat embolism. The degree of cerebral embolism was as severe in these as in the untreated ones, which succumbed without exception to the combined effects of pneumothorax and fat injection.

Accordingly, it can be assumed that it is not the severity of cerebral embolism but the degree of arterial hypoxaemia which is the most important factor leading to a fatal outcome in fat embolism.

The clinical signs and symptoms in severe acute anoxia are remarkably similar to those observed in clinical fat embolism. Both are characterized by a disturbance of consciousness, convulsive fits, pathological reflexes, and extrapyramidal motility disturbances (Környei, 1955).

The histological changes in brain tissue produced by anoxia are usually not diffuse but are focal in type, and in patients surviving long enough after the episode, perivascular petechial haemorrhagic infarcts and other lesions can be demonstrated in the brain. These are similar to those observed in fat embolism. It should be added that in patients who die in consequence of fat embolism the central capillaries of the necrotic territories are often not occluded by fat emboli.

Consequently, it may be concluded that the arterial hypoxia in clinical cases of fat embolism is the result of secondary changes in lung tissue.

Fig. 10 Severity of cerebral embolism in relation to the intravenous dose of triolein.

— normal animals; --- ligation of left pulmonary artery; -.-.- left pneumothorax.

Fig. 11 Effect of an intravenous injection of 0.47 m-equiv/kg oleic acid on plasma free fatty acid concentration (μ -equiv/l). C: control values; horizontal line: mean control value; shaded area ± 1 SD.

Fig. 12 Effect of 0.47 m-equiv/kg oleic acid on free fatty acid content of lung tissue.

The Role of Lipolysis and Its Effects on the Lungs

Anoxic lesions of the capillary wall as a factor contributing to the pulmonary changes in fat embolism were postulated many years ago by Bergmann (1863) and Ribbert (1900). However, histological changes and experimental observations are more in favour of a toxic lesion (Harris, Perret, and MacLachlin, 1939; Peltier, 1956; Rubia and Schulz, 1963; Szabó, Magyar, and Jankovics, 1968), and the agent producing this lesion is most probably free fatty acid liberated from the neutral fat trapped in the lung capillaries. Unesterified fatty acids are well known to be toxic and to produce serious lesions in the lungs.

After fracture embolic fat disappears from the lung capillaries relatively quickly, practically all within a week (Vance, 1931; Sevitt, 1962; Szabó, Jankovics, Magyar, Szabó, and Szepesházy, 1967), possibly after lipolysis by lipases present in the lung tissue. The first step in this breakdown is obviously hydrolysis to nonesterified fatty acids.

In normal lung tissue there is enough lipolytic enzyme to split the embolic fat. Calculated from experiments *in vitro*, 1 g dry lung tissue releases about 600 μ g of free oleic acid from the added triolein during a four-hour incubation period. However, the lungs of animals with fat embolism exhibit no increased lipolytic activity (Szabó *et al*, 1968).

After the intravenous injection of 0.5 ml/kg unemulsified neutral fat practically the total amount could be recovered from the lungs, but by two hours after the injection no increase in plasma triglyceride concentration was observed. Moreover, the introduction of neutral fat did not produce an increase in the free fatty acid concentration of blood plasma, lung tissue, or the brain. This is not surprising, since when non-esterified fatty acid was injected into the circulation, it was rapidly intercepted by the lungs; five minutes after injecting 0.15 ml/kg oleic acid 67.4% of the dose was found in the lungs. Studies with 131 I-labelled oleic acid revealed similar results. The labelled oleic acid or the excess free fatty acid disappeared from lung tissue very rapidly (Figs. 11 and 12). Two hours after injection the concentration of free fatty acids decreased almost to the level found in the control animals. No significant part of the administered free fatty acid reached the brain. From these results it can be concluded that during the enzymatic breakdown of the embolic fat unesterified acids are liberated progressively and are rapidly metabolized. It seems doubtful whether at any time there is a toxic amount of fatty acid present in the lung tissue. When oleic acid was administered to rabbits in divided doses, that is, only 25% of the lethal dose at six-hour intervals, the total amount that ultimately killed the animals was hardly higher than the lethal dose at a single injection. Six hours after the

injection no trace of the introduced oleic acid remained in the lungs. Accordingly, it seems that the toxic agent does not accumulate but its effects increase (Fig. 13).

Experimental fat embolism produces a substantial enlargement and increased density of the lungs. A sublethal dose of neutral fat produces microscopical congestion, much interstitial oedema, and patchy intraalveolar collections of fluid in the lungs. By two hours of injection the weight of the lungs is doubled and by 72 hours it is trebled compared with lung weights in control animals. Fluid accumulates even more rapidly after the administration of free fatty acids: after five minutes the lung weight is doubled and the maximum is attained by two hours. The weights of the liver and brain are unchanged. This fluid

accumulation is not a congestive oedema but specific tissue reaction (Fig. 14).

The administration of a moderate amount of neutral fat is followed by a progressive pulmonary oedema, but considerably smaller doses of free fatty acids produce a rapid pulmonary reaction of even greater severity. With neutral fat, the oedema is greatest at 72 hours after injection, that is, at a time when much of the embolic fat has already left the lungs. Consequently, the pulmonary oedema cannot be attributed to the capillary obstruction. A toxic lesion of the capillary wall seems a more probable explanation and is also in accordance with the microscopic findings. It is not contradicted by the absence of an elevation of fatty acid concentration in the lung tissue, because even very great amounts of unesterified fat disappear rapidly from the lungs and it could also be shown that the toxic effect is cumulative.

Fig. 13 Effect of free fatty acid administered in divided doses. Abscissa: number of animals dead at the given time. Ordinate: time after the first injection and dose of oleic acid.

Fig. 14 Increase of neutral fat content (ΔC) and of relative weight (ΔW) of lung after the intravenous injection of 0.50 ml/kg triolein. Ordinate: time after the administration of triolein.

Explanation of the Clinical Syndrome

Pulmonary fat emboli produce definite functional changes in the lungs: decrease in diffusing capacity and alveolar ventilation. These are produced not so much by the obstruction to blood flow as by the secondary tissue alterations which prolong the pathway for gas exchange (Rubin and Schulz, 1963). Accordingly, a severe arterial hypoxaemia does not develop before 24 to 48 hours after injury and this would explain the well known latent period observed in patients.

From clinical and experimental observations the mechanism leading to the development of the fat embolism syndrome may be outlined as follows. Fat droplets liberated after injury from disrupted fat cells in bone marrow enter the venous circulation and are retained, mainly by the capillaries of the lungs. In some cases of gross pulmonary fat embolism secondary changes develop which limit pulmonary gas exchange. These are possibly produced by the toxic action of free fatty acids. The perivascular haemorrhage and alveolar oedema produced combine with the obstructive effects of the otherwise unimportant pulmonary emboli and lead within a few days to serious arterial hypoxaemia. This in turn produces functional changes in the brain followed, if the anoxia persists, by morphological alterations of nerve cells. The effect of arterial anoxaemia becomes more severe when, as in the brain, local circulation is more or less severely disturbed by the occlusion of some capillaries by fat droplets.

In patients with a preexisting pulmonary disease, or when in consequence of the injury the ventilatory function has been disturbed, there is the possibility of a rapid onset of the clinical syndrome, especially as the severity of the systemic embolism is deleteriously influenced by the presence of anoxaemia.

Summary

The frequency and severity of pulmonary and systemic fat embolism was studied in 100 post-traumatic deaths and in 100 cases not related to trauma. The importance of the findings was analysed with semiquantitative histological methods and with ^{131}I -labelled fat in experimental fat embolism in rabbits. It was established that if unemulsified fat is introduced into the circulation the severity of systemic embolism does not increase linearly with the increase of the introduced dose but rather in an exponential manner. The dominant factor in systemic fat embolism is, however, not the insufficiency of the pulmonary filter. After ligation of the left pulmonary artery the introduction of the fat into the left ventricle or into the carotid artery hardly influences the lethal dose of fat or the distribution of the injected lipid.

In clinical cases of fat embolism severe arterial hypoxaemia occurs. In animals with ventilation reduced by unilateral pneumothorax fat embolism produces extreme hypoxaemia, and the lethal dose of fat is reduced to one-sixth of the original value. In these animals, especially if the fat is introduced into the arterial side of the circulation, an extremely severe systemic embolism can be observed. If the same animals are placed in an atmosphere of pure oxygen the mortality is significantly reduced but the severity of systemic/cerebral fat embolism remains unaltered.

It is concluded that arterial hypoxaemia and not systemic embolism is responsible for the clinical symptoms and for the mortality in human fat embolism. The hypoxaemia is probably produced by the toxic action on lung tissue of unesterified fatty acids. Fatty acids are probably liberated in the lungs by the enzymatic breakdown of the embolic fat. However, after the introduction of neutral fat no increase of free fatty acid concentration can be detected in circulating blood or lung tissue. Injected unesterified fat also disappears rapidly from the circulation and from the tissues. Nevertheless, there is possibly a cumulative toxic action of free fatty acids liberated progressively in the lungs.

The genesis of the pulmonary changes is likely to be a toxic action by free fatty acids since, after neutral fat injections, the lung changes attain their maximum severity at a time when the major part of the embolic fat has already disappeared from their capillaries.

References

- Armin, J., and Grant, R. T. (1951). Observations on gross pulmonary fat embolism in man and the rabbit. *Clin. Sci.*, **10**, 441-469.
- Bergmann, E. (1863). *Zur Lehre von der Fettembolie*. Thesis. Karow, Dorpat.
- Cobb, C. A., Jr., LeQuire, V. S., Gray, M. E., and Hillman, J. W. (1958). Therapy of traumatic fat embolism with intravenous fluids and heparin. *Surg. Forum*, **9**, 751-756.
- Collins, J. A., Hudson, T. L., Hamacher, W. R., Rokous, J., Williams, G., and Hardaway, R. M. (1968). III: Systemic fat embolism in four combat casualties. *Ann. Surg.*, **167**, 493-499.
- Evarts, C. M. (1965). Diagnosis and treatment of fat embolism. *J. Amer. med. Ass.*, **194**, 899-901.
- Gröndahl, N. B. (1911). Untersuchungen über Fettembolie. *Dtsch. Z. Chir.*, **131**, 56-124.
- Harris, R. I., Perrett, T. S., and MacLachlin, A. (1939). Fat embolism. *Ann. Surg.*, **110**, 1095-1114.
- Kolmert, F. (1939). A few observations on fat embolism. *Acta chir. scand.*, **83**, 263-268.
- Környei, I. (1955). *Histopathologie und klinische Symptomatologie der anoxisch-vasalen Hirnschädigungen*. Akadémiai Kiadó, Budapest.
- Maruyama, Y., and Little, J. B. (1962). Roentgen manifestations of traumatic pulmonary fat embolism. *Radiology*, **79**, 945-952.
- Nagy, E., Serényi, P., and Szabó G. (1970). Die Röntgendiagnose der Fettembolie. In press.
- Peltier, L. F. (1956). Fat embolism. III. The toxic properties of neutral fat and free fatty acids. *Surgery*, **44**, 665-670.
- Peltier, L. F. (1957). An appraisal of the problem of fat embolism. *Int. Abstr. Surg.*, **104**, 313-324.
- Ribbert, H. (1900). Zur Fettembolie. *Dtsch. med. Wschr.*, **26**, 419-421.
- Robb-Smith, A. H. T. (1941). Pulmonary fat embolism. *Lancet*, **1**, 135-141.
- Rubia, F. J., and Schulz, H. (1963). Elektronenmikroskopische Untersuchungen des Blut-Luft-Weges bei der experimentellen Fettembolie der Lunge. *Beitr. path. Anat.*, **128**, 78-102.
- Scriba, J. (1880). Untersuchungen über die Fettembolie. *Dtsch. Z. Chir.*, **12**, 118-219.
- Sevitt, S. (1960). Significance and classification of fat-embolism. *Lancet*, **2**, 825-828.
- Sevitt, S. (1962). *Fat Embolism*. Butterworths, London.
- Sproule, B. T., Brady, J. L., and Gilbert, J. A. L. (1964). Studies on the syndrome of fat embolism. *Canad. med. Ass. J.*, **90**, 1243-1247.
- Szabó, G., Jankovics, R., Magyar, Z., Szabó, A., and Szepesházy, K. (1967). The pathomechanism of fat embolism. I. Comparative quantitative study of human and experimental fat embolism. *Acta med. Acad. Sci. hung.*, **24**, 299-313.
- Szabó, G., Magyar, Z., and Jankovics, R. (1969a). The pathomechanism of fat embolism. III. The effect of reduced respiratory surface on lethality. *Acta med. Acad. Sci. hung.*, **26**, 1-11.
- Szabó, G., Magyar, Z., and Jankovics, R. (1968). Fatty acid poisoning as a possible factor producing the syndrome of fat embolism. *Acta med. Acad. Sci. hung.*, **25**, 331-343.
- Szabó, G., Jankovics, R., and Farkas, G. (1969b). The pathomechanism of fat embolism. IV. Cerebral and pulmonary factors in the fat embolism syndrome. *Acta med. Acad. Sci. hung.*, **26**, 143-155.
- Traumann, K. J., and Wetzel, U. (1962). Röntgenologische Lungenveränderungen bei der Fettembolie. *Med. Klin.*, **57**, 2098-2100.
- Vance, B. M. (1931). The significance of fat embolism. *Arch. Surg.*, **23**, 426-465.
- Wertberger, J. J., and Peltier, L. F. (1968). Fat embolism. The importance of arterial hypoxia. *Surgery*, **63**, 626-629.
- Whiteley, H. J. (1954). The relation between tissue injury and the manifestations of pulmonary fat embolism. *J. Path. Bact.*, **67**, 521-530.