Genesis of fat emboli

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In pathological terms fat embolism may be defined as the blockage of blood vessels by liquid fat globules. As Szabó (1970) emphasizes, on page 123 of this issue, a clear distinction must be drawn between the histopathological findings and the much less common clinical syndromes of fat embolism. Fat emboli in the lungs have been reported in a great variety of associations, but by far the most common and the most important association is with major fractures and accompanying soft tissue damage due to severe trauma. Controversy exists regarding the clinical significance of the emboli and there is even a suggestion that they are not essential for the changes underlying the 'fat-embolism' syndrome. This is one of the many anomalies with which this intriguing condition is beset.

A wide divergence of opinion exists regarding the genesis of fat emboli. According to the classical 'mechanical' explanation fat droplets are set free from disrupted fat cells, enter torn venules at sites of injury or fracture, and are carried to the lungs. Globules 10 μ or more in diameter being unable to pass immediately through the lung capillaries are retained as emboli. The alternative explanation, which also has many adherents, envisages fat emboli as derived partly or entirely from plasma lipids, possibly after increased mobilization from depot fat. If prophylactic and therapeutic measures are to be well founded, it is important to ascertain which explanation is correct.

Fat emboli are initially arrested in the lungs which act as a filter to protect the systemic circulation. They have certain peculiarities *qua* emboli. Often they are very numerous: in the most heavily embolized lungs thousands of emboli per cubic millimetre of lung tissue may be seen. They are relatively small: their diameter in lung vessels ranges from about 10 to 100 μ , and therefore they lodge in capillaries and arterioles.

Some may be stuck fast, but there is evidence that others continue to flow slowly through the small vessels and recirculate, returning eventually to the lungs (Scriba, 1880; Scuderi, 1953; Moseley and Wurnig, 1954). When the lungs are heavily embolized, the globules passing through the lung vessels into the systemic circulation may become very numerous. Possibly this is the most serious consequence because of the multifocal brain damage which results from cerebral embolization (Scriba, 1880; Sevitt, 1962) and may in turn lead to secondary lung changes. But some would give pride of place to the pulmonary changes and regard the cerebral damage as secondary to hypoxaemia (Peltier, 1967; Szabó, 1970).

Aetiology of Fat Embolism

INJURY TO ADIPOSE TISSUE AND TO BONE MARROW

Leaving aside trivial or low-grade pulmonary fat embolism, a common incidental finding at necropsy, much the most important association is with fractures and soft tissue damage. This was recognized early and has been amply corroborated. Certain fractures, such as those of long bones, pelvis, or spine, are more prone than others to be followed by severe pulmonary fat embolism (Fig. 1). Further, the intensity of fat embolization tends to be directly related to the severity of injury, and especially to multiplicity of fractures (Emson, 1958; Sevitt, 1962). Histological fat embolism can occur with remarkable rapidity and even very severe (grade 4) lung involvement may be found occasionally in those who die 'immediately' after injury.

Jarring of the skeleton has been said to cause significant fat embolism but this is doubtful.

Fig. 1 Severity of histological pulmonary fat embolism at necropsy related to fractures.

Each point, or vertically joined series of points, represents one subject in a necropsy series of 43 fracture cases. Certain fractures, particularly of the shaft of femur, other long bones, and pelvis, and multiple fractures in general, tend to result in severe (grades 3 and 4) fat embolism. Most (21/32) of the isolated fractures are associated with lesser grades (0, 1, and 2) of embolism. Some of the apparent anomalies are attributable either to very short or to prolonged survival.

and although cases are reported from time to time (Beitzke, 1912; Silverstein and Konzelman, 1940), it is well known that fractures can be overlooked even at necropsy. Such an oversight may also account for instances of fat embolism attributed to convulsions (Meyer and Teare, 1945).

It is surprising how rarely clinical fat embolism results from surgical injury to bone marrow such as intramedullary nailing (Scuderi, 1953). Embolization of fat and marrow tissue may follow external cardiac massage with injury to the ribs and sternum, and in some instances this is an agonal if not actually a postmortem occurrence (Sack and Wegener, 1968). An unusual cause of fat embolization is infarction of the bone marrow in cases of sickle-cell anaemia (Vance and Fisher, 1941; Wyatt and Orrahood, 1952). In dogs, decompression sickness following exposure to hyperbaric conditions may be accompanied by pulmonary fat and marrow embolism secondary to disruption of the bone marrow by gas bubbles, but it is uncertain whether this is an important feature of decompression sickness in man (Bennison, Catton, and Fryer, 1965).

Injury to the soft tissues seldom causes severe fat embolism though cases have been reported (Scully, 1956). Severe pulmonary and systemic embolism were seen in a 64-year-old man who died 10 days after the second of two operations for aneurysm of the abdominal aorta. Personal observations confirm Gröndahl's (1911) opinion that severe burns cause only insignificant fat embolism. Acute pancreatic necrosis has been reported as a cause (Edmondson and Fields, 1942; Lynch, 1954), but a personal study of eight fatal cases failed to confirm this. In a fatal case of Weber-Christian disease the occurrence of fat embolism was attributed to the necrotizing process in adipose tissue (Miller and Kritzer, 1943). A fatty liver may be regarded in the present context as a form of adipose tissue from which embolic fat might be liberated by trauma (Gröndahl, 1911; Killian, 1931; Hallgren, Kerstell, Rudenstam, and Svanborg, 1966), by necrosis (MacMahon and Weiss, 1929; Tonge, Hurley, and Ferguson, 1969), or even spontaneously (Cammermeyer and Gjessing, 1951; Hartroft and Ridout, 1951; Kent, 1955; Lynch, Raphael, and Dixon, 1959). Nevertheless, the liver is seldom if ever a significant source of embolic fat.

INGRESS OF FREE LIQUID FAT INTO THE BLOODSTREAM

Observations at operation or at necropsy confirm that liquid fat is freed at fracture sites where the marrow is fatty. Some of the freed fat may be derived from adjacent adipose tissue (*vide infra*). As originally envisaged, the embolic process required a pool of liquid fat, venules with gaping ends held open by attachment to bony canals (Gauss, 1916), and an impelling force provided by local increase in extravascular pressure due to haemorrhage at the fracture site (Flournoy, 1878). Later it was found that the venules in bone marrow are not incapable of collapsing (Urist and Johnson, 1943; Whitson, 1951) and that fracture leads to a fall in intramedullary pressure (Rehm, 1956 and 1957; Szabó, Jankovics, and Magyar, 1967).

The process of embolism was illuminated by the work of Young and Griffith (1950) who studied its dynamics using a model representing a thin-walled blood vessel suspended in a fluid medium. As the pressure within the 'vessel' fell below the external pressure there was a rapid alternation of collapse and re-expansion. During each re-expansion phase small plastic spherules within the supporting medium were drawn into the lumen of the 'vessel' through a slightly larger hole previously made in its wall. Fuchsig, Brücke, Blümel, and Gottlob (1967) found that liquid fat injected subcutaneously or intramuscularly was rapidly mobilized into the bloodstream following the induction of haemorrhagic shock. Presumably this is determined by a critical reduction of intravascular relative to extravascular pressure.

An extreme fall in intravascular pressure following cardiac arrest may also account for the high incidence of fat and bone-marrow embolism after external cardiac massage (Sack and Wegener, 1968).

According to Fuchsig *et al* (1967) the main route of ingress for the fat was through the lymphatic system into the innominate vein, but the evidence for this is tenuous. If any fat reaches the bloodstream via the lymphatics the amount is likely to be unimportant (Szabó, Serényi, and Kocsár, 1963). The idea is of historical interest in that thoracic duct drainage was once advocated as a prophylactic measure. Pulmonary and cerebral oil embolism have been reported following lymphangiography (Fabel, Kunitsch, and Stender, 1967; Davidson, 1969), but the route may be directly from lymphatics into adjacent veins (Bron, Baum, and Abrams, 1963).

MINIMUM LETHAL DOSE OF EMBOLIC FAT

If the mechanical concept of pathogenesis is valid, enough freed fat has to be available at fracture sites to match the quantities found in the lungs and other organs in the most severe cases. Some believe that the amount is inadequate and look for other explanations. An estimate of the minimum lethal dose of intravenous fat in man is needed. The problem may be tackled by reference to case reports of iatrogenic embolism; by estimating the embolic fat content of the lungs in fatal cases; and by extrapolation from the minimum lethal dose of fat injected intravenously in experimental animals.

Differences in chemical and physical properties of the oil may influence the minimum lethal dose in iatrogenic embolism. In 1824 an American physician injected 15 ml of castor oil into a vein in his forearm and survived (Sevitt, 1962), and a century later the survival of a patient following intravenous injection of 24 ml of human oil was reported by Koch (1924). But death from cerebral embolism has been reported after intravenous injection of less than 50 ml of olive oil (Fibiger, 1900), and less than 30 ml of cottonseed oil (Carr and Johnson, 1935). In other cases reported the cause of death was uncertain as was the

amount of oil which actually entered the venous system.

Estimates of the quantity of embolic fat in the lungs of patients who died after developing the fat-embolism syndrome have been attempted although normal lungs contain adipose tissue and other sources of lipid, and the amount varies widely. The values range from about 20 ml (Killian, 1931), through 36 ml (Armin and Grant, 1951) to the probable overestimates of Elting and Martin (1925). Assuming that 20% of the embolic fat may have passed into the systemic circulation, then the total quantity would be 24 to 43 ml, or 0.3 to 0.6 ml per kg in a 70-kg man.

The Tables show estimates of the minimum lethal dose of various oils injected intravenously into animals and also indicates a species difference in tolerance. Experimental lethality also depends on the rate of injection, the use of single or divided doses, and the time interval between successive doses. Viscosity of the oil is probably important. The relative tolerance of man is unknown and extrapolation from animal findings may be misleading. If these considerations are ignored, extrapolation indicates that the minimum lethal dose for a 70-kg man is between 50 and 154 ml. But there may also be much individual variation in tolerance. Only 0.3 ml per kilogram body weight was found lethal for some rabbits (Krönke, 1957) and the proportional amount for a man would be about 20 ml.

Traumatic or posthaemorrhagic shock appears to increase the sensitivity of animals to intravenously injected fat (Harman and Ragaz, 1950; Moser and Wurnig, 1954; Whiteley, 1954); the emboli in the lungs are fewer but larger, lying within arterioles rather than capillaries. Experimentally the minimum lethal dose may be reduced by a factor of 3 (Moser and Wurnig, 1954) and there is circumstantial evidence that a similar state of affairs obtains in man (Fig. 2). The contrary findings of Armin and Grant (1951) can probably be discounted since their rabbits were injected with only small amounts of fat (0.15 ml per kg body weight) before the induction of haemorrhagic shock.

Given intravenously a fatty acid such as oleic acid is more harmful to the lungs than a corresponding dose of the triglyceride (Harris, Perret, and MacLachlin, 1939). Consequently the minimum lethal dose of embolic fat would be reduced if it contained fatty acids liberated at the site of injury (Scuderi, 1953) or released within the lung after embolism by the action of pulmonary lipase (Harman and Ragaz, 1950). The latter idea has been strongly supported by Peltier (1956b and 1967) and is not implausible, but remains unproven (Collins, 1969). Intravenously oleic acid has been widely used to produce an experimental model of the fat-embolism syndrome in animals (Ashbaugh and Uzawa, 1968; Szabó, Magyar, and Jankovics, 1968; Wertman,

Experimental Animal	Embolic Material	Minimum Lethal Dose (ml/kg body weight)	Author(s)
Dog	Cottonseed oil	1.5	Lehman and Moore (1927)
Dog	Liquid dog fat	2.0	Halasz and Marasco (1957)
Dog	Olive oil	2.2	Scuderi (1941)
Dog	Oleic acid	0.33	Scuderi (1941)
Rabbit	Olive oil	0.7	Sessner <i>et al</i> (1961)
Rabbit	Liquid rabbit fat	0.8	Krönke (1957)
Rabbit	Liquid rabbit fat	0.9	Harman and Ragaz (1950)
Rabbit	Human marrow fat	0.9	Harris <i>et al</i> (1939)
Rat	Arachis oil	1.0	Whiteley (1954)

Table Minimal lethal doses of intravenously injected oils and fats¹

¹The dog appears more tolerant to neutral fat than the rabbit or rat, and oleic acid is much more lethal than neutral fat.

Fig. 2 Lung from a man aged 48 years who died 36 hours after multiple fractures of the pelvis and left tibia. Large fat emboli in precapillary vessels, but absent from alveolar capillaries. The degree of embolism is only grade 2 in terms of numbers of emboli, but the largest embolus is alone equivalent in volume to 450 or more rounded fat globules of 20 μ diameter. Patient probably in state of traumatic shock when embolization occurred. Frozen section, Sudan $\times 100$.

berger and Peltier, 1968; Baker, Kuenzig, and Peltier, 1969), but the admissibility of this model must be questioned. Nevertheless, intravenous injection of neutral fat is followed by an increased lipase activity of the blood said to be derived from the lungs (Peltier and Scott, 1957). Estimation of blood lipase is claimed to be of possible diagnostic value (Peltier, 1965), but this is disputed (Ross, 1969).

QUANTITY OF POTENTIALLY EMBOLIC FAT AVAILABLE AT FRACTURE SITES

From estimates of the fat content of animal bones Scriba (1880) calculated that the adult human femur contains some 70 ml of fat. By measurement of the marrow cavity Lehman and Moore (1927) arrived at a figure of about 65 ml. By extracting the fat with solvents, Peltier (1956a) found that the metaphyses of two human femora contained about 81 ml and 114 ml respectively. Liberation of this quantity into the bloodstream would doubtless prove fatal, and it was found that intravenous injection of the fat from one rabbit femur into another rabbit caused death

nine times out of 10 (Glas, Musselman, and Davis, 1955).

A false construction must not be put on these findings, since even in severe fractures the marrow is disrupted only around the fractured area. Nevertheless, Vance (1931) claimed to find up to 60 ml of freed fat at the sites of long leg bone fractures, though some may have been derived from traumatized adipose tissue around the bone. In one case Palmovic and McCarroll (1965) found about 30 ml of oil in lacerated subcutaneous tissue around a fractured sternum. More information is needed on the quantities of fat freed at and around fracture sites at different intervals after injury. In this connexion, claims have been made that fat embolism is more common in obese subjects (Alexander-Katz, 1924) and that the histological severity of fat embolism is greater in obese than in lean rabbits (Swank and Dugger, 1954). On the other hand Warren (1946) found no association with obesity in man and this has been my experience. Even if there were, its existence could be obscured by the more important factors of the multiplicity and severity of fractures.

FAT EMBOLISM IN CHILDREN

Traumatic fat embolism is reported (Landois, 1926) to be rare in children below the age of 10 years although it has been described (Carty, 1957), even in the newborn (Nicod, 1938). I have found severe (grade 3) pulmonary fat embolism in a 2-year-old boy who died seven hours after sustaining a fractured skull and extensive soft tissue contusions. The rarity of severe cases in childhood may be related to the dearth of frankly fatty marrow in long bones until about 7 years of age. Kane, Peller, Rudolph, and Fink (1961) found difficulty in producing fat embolism by femoral fracture in very young female rabbits, although the procedure was very reliable in adult male rabbits. Further, marrow fat in children is said to contain relatively less olein and a greater proportion of the more viscous stearin and palmitin (Bürger, 1915). If these characteristics are chiefly responsible for the infrequency in childhood, then *per contra* an important role can be adduced for the fatty marrow in adults.

BONE-MARROW EMBOLISM

Bone-marrow embolism can occur very rapidly after trauma, and both marrow and fat emboli are often seen in those who die after having received external cardiac massage. However, marrow emboli tend to break up and lose their identity after a few hours (Mason, 1968) and it is probably this which has concealed the regularity of their association with embolic fat. Mason (1968) found lung fat emboli in 60% and marrow emboli in 30% of a large series of aviation deaths, and marrow emboli were never seen

without fat emboli. If the embolic route is open to marrow fragments there is no reason to suppose that it is not also open to freed liquid fat.

Concept of Fat Embolism as a Disorder of Lipid Metabolism and Transport

Many workers have been attracted to the concept of fat embolism as a disturbance of lipid metabolism and transport. The idea has several versions but all postulate that plasma lipids provide the immediate source of the intravascular globules. Some hold that these globules are not even embolic but form *in situ* by a process allied to thrombosis. Whether these views be accepted or not, and there is much evidence against them, they have provided an impetus to research.

THE PLASMA LIPIDS

Since Lehman and Moore (1927) first suggested that fat embolism results from coalescence of chylomicrons, knowledge of the plasma lipids has greatly increased (Pilkington, 1964; Fredrickson, Levy, and Lees, 1967). In fasting subjects the plasma lipid content is between 300 mg and 800 mg per 100 ml; after a fatty meal and in certain disorders of lipid metabolism it is greatly increased. The main plasma lipids are cholesterol (esterified and nonesterified), phospholipids, glycerides (largely triglycerides of oleic, palmitic, and linoleic acids), and nonesterified fatty acids (Nefa). All are insoluble in water, but most of the Nefa forms a soluble complex with albumin while the other lipids interact with specific proteins to form soluble macromolecules known as lipoproteins.

A distinction should be drawn between plasma lipid concentration and the quantity transported through the plasma. The transport of Nefa, derived from adipose tissue triglycerides, to various sites of utilization is predominant; more than 25 g can be transported daily. When the flux of Nefa to the liver exceeds its powers of utilization, it is re-esterified to triglyceride. This results in endogenous lipaemia involving the pre-beta or very low density lipoprotein. Milkiness of the plasma is due to the presence of lipid particles sufficiently large (>0.1 micron) to scatter light.

Glyceride transport is next in magnitude. Glycerides of endogenous origin are synthesized in the liver and removed from the plasma at a rate of 2 g per hour. Ingested glycerides (1 g to 2 g per kg body weight per day) reach the bloodstream via the thoracic duct as chylomicrons, 0.1 to 1.0μ in diameter. These consist of 99% lipid, most of it glycerides with about 4% cholesterol or cholesterol-ester. Chylomicrons are rapidly removed from the plasma, the half time being

five to 15 minutes. This is due to hydrolysis by heparin-activated lipoprotein-lipase and is followed by incorporation of the fatty acids into adipose tissue cells where they are re-esterified. Intravenous heparin releases lipoprotein-lipase which clears lipaemic turbidity. Another lipase in adipose tissue is activated by catecholamines and releases free fatty acids (Nefa) into the bloodstream.

The main cholesterol bearers in man are the beta-lipoproteins and the daily turnover is small. The main role of plasma cholesterol and phospholipids is to help to transport other lipids.

CHANGES IN BLOOD LIPIDS FOLLOWING HAEMORRHAGE AND TRAUMA

Posthaemorrhagic lipaemia was first described in rabbits subjected to repeated daily bleedings (Boggs and Morris, 1909). Subsequently lipaemia was also found in animals after trauma such as tourniquet shock and crushing of limbs (Johnson and Svanborg, 1956; Johnson and Wadström, 1956), burns (Harvengt, 1961), femoral fracture, and laparotomy (Carlson and Liljedahl, 1963). Similar changes in blood lipids also occur in man after injury (Wadström, 1959; Durst, Eggstein, Flach, Geisbe, Knodel, and Probst, 1968) and may be regarded as part of the general metabolic response to trauma (Sevitt, 1966). The changes are complex but there is evidently an enhancement of lipokinesis with an increased flux of Nefa from the peripheral stores which soon show evidence of depletion.

Raised catecholamine secretion probably contributes to this phenomenon (Carlson, Liljedahl, and Wirsén, 1965), noradrenaline being more potent than adrenaline in provoking a prolonged increase in lipid mobilization (Havel and Goldfien, 1959). Protracted catecholamine infusion in dogs caused heavy intracellular deposition of triglycerides in the liver, but fat globules were not found in the lung vessels (Eltringham, Jenner, and Morgan, 1969).

Lung fat emboli appear very rapidly after fractures and it is difficult to envisage this as a result of disturbed lipid metabolism (Krönke, 1956) although that is the basis of traumatic lipaemia. Sevitt (1962 and 1966) has emphasized that there are no grounds for equating traumatic lipaemia with fat embolism, though both may occur together, and the synonymous use of the terms (Warthin, 1913) should be discouraged. Changes in the blood triglyceride content have no bearing on the genesis of fat emboli, though a partial redistribution between the plasma and the erythrocytes has been demonstrated within 30 minutes of femoral fracture in dogs (Bergentz, 1961 and 1968). Triglycerides trapped within masses of sludged erythrocytes should not be confused microscopically with fat emboli, as is clear from histological examination of corresponding paraffin sections (Fig. 3).

FAT MACROGLOBULES IN THE BLOOD

After injury and operation fat globules, 5 to 20 μ in diameter, have been demonstrated in the blood and finding these has been advocated as a diagnostic procedure (Scuderi, 1941). But similar globules may be found in uninjured controls, so they may be a normal occurrence (Bryans and Eiseman, 1956; Bergentz, 1961; Davies and Peltier, 1961). Tedeschi, Castelli, Kropp, and Tedeschi (1968) found fat globules of this size almost as often in healthy people or patients with medical conditions as in those with extensive trauma to bone and adipose tissue. The incidence in the different groups ranged from 18 to 30% and was 40% after cardiac massage. 'Fat macroglobulaemia' seems an apt name for this phenomenon though the large fat globules may be an artefact developing after withdrawal of the blood sample, especially as the plasma is often dried before examination.

Demonstration of fat macroglobules has no diagnostic value in suspected cases of fat embolism nor for detecting subclinical cases. Although Gurd (1969a and b) has recently revived this idea, using a millipore filter with a pore size of 8 μ to segregate the larger fat globules, no mention is made of control studies. Bergentz (1961) suggested that fat macroglobules are

derived from chylomicrons and this is supported by the results of analytical studies (Tedeschi *et al.*, 1968). Whatever their genesis, fat macroglobules might account for the common incidental finding of low-grade pulmonary fat embolism at necropsy.

AGGREGATION AND COALESCENCE OF CHYLOMICRONS

The plasma lipid particles form a very stable emulsion and only rather drastic methods, such as the addition of ether and other fat solvents (Lehman and Moore, 1927), destroy this stability *in vitro*. Ether anaesthesia was once incriminated as a cause of pulmonary fat embolism in man (Watson, 1937), but more recent observations using lipaemic dogs have failed to confirm this (Davies and Peltier, 1961). The alpha-toxin of *Cl. welchii* causes flocculation of chylomicrons *in vitro* (Elkes and Frazer, 1943) and fat embolism has been reported as a complication of gas gangrene (Govan, 1946). However, it is rarely important (Robb-Smith, 1945; Palmovic and McCarroll, 1965) and the few fat emboli which appear are more likely to originate from fat liberated from adipose tissue than from chylomicrons (Frazer, Elkes, Sammons, Govan, and Cooke, 1945). Rats subjected to hind limb ischaemia showed no evidence of chylomicron flocculation, and experiments *in vitro* with extracts of ischaemic muscle also gave negative results (Whiteley, 1954). Increased secretion of adrenocortical hormones due to the stress of injury was put forward as a cause of chylomicron flocculation (Glas, Grekin, and Musselman, 1953) but this could not be confirmed experimentally (Glas, Grekin, Davies, and Musselman, 1956). Occasional reports appear in which fat embolism is attributed to the long-term administration of corticosteroids (Moran, 1962; Jones, Engelman, and Najarian, 1965; Hill, 1969), but severe fatty change in the liver is probably more relevant.

Fat macroglobulaemia and a combination of pulmonary and systemic fat embolism have been described after cardiac surgery involving the use of an extracorporeal circulation (Owens, Adams, and Scott, 1960; Lee, Krumhaar, Fonkalsrud, Schjeide, and Maloney, 1961; Miller, Fonkalsrud, Latta, and Maloney, 1962; Wright, Sarkozy, Dobell, and Murphy, 1963; Evans and Wellington, 1964) and denaturation of lipoproteins leading to lipid aggregation has been postulated. On the other hand, the procedure involves transection of the sternum and damage to intra-thoracic adipose tissue, and this could account for the embolic fat. Such special circumstances apart, any hypothesis concerning the origin of fat emboli from plasma lipids must take into account that pulmonary fat embolism precedes and is often unaccompanied by systemic involvement.

Fig. 3 Severe pulmonary fat embolism in paraffin section. The fat emboli have been dissolved out during processing leaving empty spaces which retain the shape of the emboli. There is nothing to suggest that erythrocytes, platelets, or fibrin formed a component of the emboli. Patient died four days after crush fracture of pelvis. Haematoxylin and eosin $\times 175$.

EFFECT OF HYPERLIPAEMIA ON FAT EMBOLISM

Reports (Swank, Glinsman, and Sloop, 1960; Weld, 1948) that pulmonary fat embolism is a normal accompaniment of alimentary lipaemia need be given little credence and have not been confirmed (Watson, 1960). There have been no reports of spontaneous fat embolism in cases of idiopathic hyperlipoproteinaemia with milky plasma and plasma lipids sometimes exceeding 10 g per 100 ml. At necropsy some diabetics showed pulmonary fat embolism, but this was rarely severe and possibly related to fatty liver rather than to secondary hyperlipaemia (Kent, 1955; Watson, 1960). Intravenous infusion of a stable fat emulsion does not cause fat embolism in man or in animals (Adkins, Foster, and O'Saile, 1962).

Reports on the effects of hyperlipaemia on the degree of post-traumatic fat embolism produced experimentally have been conflicting. Some workers (Peltier, 1955; Brody, Meadows, and Zaronetis, 1964) found that it had no effect, whereas Bergenz (1961) found more pulmonary fat emboli after injury in hyperlipaemic than in control animals, but only during the first hour after injury. The 'trigger' hypothesis of Glas *et al* (1955) still awaits corroboration: this envisages transformation of the plasma lipids into discrete globules by the entry from injured marrow of relatively few fat globules.

CHANGES IN BLOOD COAGULABILITY AND FAT EMBOLI

Fat emboli have been described in animals following intravenous injection of thromboplastic substances or thrombin (Bergentz, 1961; Adkins *et al*, 1962) or by induction of a generalized Schwartzman reaction (Allardyce and Groves, 1969). However, the 'emboli' illustrated do not have circumscribed outlines and bear no convincing resemblance to those seen in human pathology. Microthrombi in the lungs or glomeruli are only occasionally associated with embolic fat (Eeles and Sevitt, 1967) although examples have been reported (see citations by Sessner, Schütterle, and Stummeyer, 1961). The rounded hyaline fibrin bodies described by Serck-Hanssen (1965) as a feature of cerebral fat embolism are not specific. They are a reaction to brain damage, probably related to thromboplastin diffusing from degenerate perivascular myelin (Woolf, 1952).

Nevertheless, severe injury in man (Innes and Sevitt, 1964) and animals (Bergentz, 1961) is followed by changes in blood coagulability, and similar changes are claimed after intravenous injection of olive oil in rabbits (Sessner *et al*, 1961). An initial transient phase of hypercoagulability and enhanced fibrinolytic activity and a more prolonged fall in the platelet count are characteristic after trauma. These changes are

not necessarily related to the entry of a tissue thromboplastin as similar changes occur in bled animals without trauma and may be initiated by release of catecholamines (Roberts, 1970). Using radioiodine-labelled fibrinogen and lung scanning to detect thrombi, Saldeen (1969a and b) found that the radioactivity over the lungs rapidly increased after fracture of leg bones or injection of homogenized adipose tissue in rats. This increase was transient, probably due to local fibrinolysis. The significance of these findings in relation to the genesis of fat embolism is unclear.

There is no doubt that some of the clinical conditions which produce fat embolism also produce complex changes in blood coagulability and related rheological changes, but these can be separated. The view (Bergentz, 1968) that flow and coagulation changes are the cause of the fat embolism syndrome, and that the syndrome may occur without fat emboli, is likely to cause and aggravate confusion.

The Nature of Embolic Fat

Too little attention has been paid to the nature and chemical composition of the embolic fat although this is a key issue since composition will reflect origin. Histochemical and special chemical techniques have been applied to the problem but more are needed.

HISTOCHEMISTRY

In frozen sections fat emboli are deeply coloured by the red Sudan dyes dissolved in a suitable solvent, and their colouration is indistinguishable from that of adipose tissue cells. Other biological lipids which take up the colorant, such as fatty acids, cholesterol in liquid state, and complex tissue lipids, stain less intensely or with a rather different colour. Sudan black B also colours neutral fats but its main value is to demonstrate phospholipids. Fat emboli and depot fat blacken when exposed to osmium tetroxide, the reaction depending on the presence of the unsaturated olein. Certain fluorochromes such as Phosphine 3R have been used to demonstrate fat emboli (Kane *et al*, 1961). It has the advantage of being used in aqueous solution, but fluorescence microscopy with an ultraviolet light source is required and may be combined with dark field microscopy (Tedeschi *et al*, 1968). Nile Blue sulphate, also used in aqueous solution, stains triglycerides a pink or red colour but it cannot be relied on to distinguish triglycerides from free fatty acids as was once claimed.

All these techniques indicate the high triglyceride content of fat emboli, but this does not mean that other lipids are not present. LeQuire, Shapiro, LeQuire, Cobb, and Fleet (1959) claimed to find histochemical evidence of cholesterol in

Fig. 4 A profusion of intravascular fat globules in lung tissue from a case of severe (grade 4) embolization: (left) ordinary light microscopy; (right) same field under the polarizing microscope. Aggregates of birefringent crystalline material occur in most of the emboli. The crystals are Schultz-negative and closely resemble those seen in adipose tissue cells. Frozen section, Sudan $\times 250$.

lung fat emboli in nine human cases. The emboli stained as expected with Sudan IV and Nile Blue sulphate, but contained birefringent crystals arranged in sheaf-like forms. The birefringence disappeared at 60°C but reappeared on cooling. The crystals were soluble in fat solvents; both the crystalline and noncrystalline components of the emboli gave a positive Schultz histochemical reaction for cholesterol based on the Lieberman-Burchardt sterol reaction, and other findings suggested that some of the cholesterol was present in ester form. The sensitivity of the Schultz test is low (Reiner, 1953) and the positive reaction implied a cholesterol concentration of 10 to 30% in the fat emboli. Not unreasonably plasma fat was suggested as the source of the emboli.

In view of the importance of these findings an independent investigation was carried out in 22 cases of pulmonary fat embolism of all grades of severity, nearly all with fractures (Ellis and Watson, 1966 and 1968). Survival times ranged from rapid death to 22 days after injury. In six subjects there was systemic involvement which was clinically apparent in three. Birefringent crystals similar to those described by LeQuire *et al* (1959) were observed in each case, usually in most of the embolic fat globules (Fig. 4). However, neither the crystals nor the non-crystalline portion of the emboli gave a positive

Schultz histochemical reaction for cholesterol. Furthermore, the fat of adipose-tissue cells, including bone marrow, also contained crystals apparently identical with those seen in the fat emboli. These crystals in adipose tissue cells are not a technical artefact and must be a normal constituent which crystallizes on cooling. They disappear partly on warming to 30°C and completely at 60°C. The use of a warm mounting medium such as glycerol jelly may temporarily retard the development of the crystals in sections. X-ray diffraction analysis might be expected to establish their precise nature (Prokš and Valvoda, 1966). The regular development of similar crystals in fat emboli favours their origin from marrow fat or adipose tissue.

LeQuire (1966) failed to demonstrate Schultz-positive emboli in sections from the cases of Ellis and Watson, although they confirmed the presence of Schultz-positive fat emboli in a small block of formalin-fixed lung from one of his cases (Ellis and Watson, 1968). Such emboli seem to be very unusual, and further confirmation of their occurrence is desirable. Cases with a mixed population of triglyceride emboli and triglyceride-cholesterol emboli may also be possible. Attempts to increase the cholesterol content of marrow fat *in vitro* by admixture with a purified preparation of beta-lipoprotein were unsuccessful (Ellis and Watson, 1969), but this does not preclude the uptake of cholesterol *in vivo*. A patient with multiple fractures and the fat-embolism syndrome is claimed to have shown absence of pre-beta lipoprotein from the serum for seven days after injury, until clinical improvement took place (Hillman and LeQuire, 1968). Emboli formed from or enriched by this lipoprotein might give a positive Schultz reaction.

LeQuire *et al* (1959) also observed crystals and a positive Schultz reaction in lung fat emboli induced in rabbits by subatmospheric decompression. However, this is an ineffective or unreliable means of producing experimental pulmonary fat emboli, and the few emboli that occur have been found by others to be Schultz-negative (Ellis and Watson, 1969).

CHEMICAL ANALYSIS OF LUNG FAT

Holczabek (1964) extracted the fat from the lungs of patients with fractures and related the fat content to the degree of histological embolism. When the lipid content exceeded 200 mg per 100 g of wet lung tissue fat emboli were always present and were usually numerous. Using thin-layer chromatography for analysis, the highest concentrations of triglyceride were found when the lipid content was highest and the degree of histological embolism was greatest. The triglyceride content of the extracted lipid averaged 61% in those with most lung emboli and ranged up to 78%. Holczabek (1964) concluded that the findings could only be accounted for by an incursion of triglyceride fat into the lungs and not by the entry of plasma lipids. These results are consistent with the classical mechanical concept.

A nonsolvent lipid extraction technique based on flotation of lipid from a 10-g sample of thinly sectioned lung tissue was used by Hillman and LeQuire (1968). The lungs of 17 patients were examined. In the five patients with severe fat embolism the total lipid recovered ranged from 2.3 to 20.1 mg per 10 g weight of lung, and its cholesterol content ranged from 5.4 to 11.0%. In three instances the recovered lung fat was examined by thin-layer chromatography and found to have a greater proportion of free cholesterol, cholesterol esters, and phospholipid than depot fat. Some of the recovered fat may have been plasma lipid however, and about 1.0 ml of plasma would account for the highest percentage of cholesterol obtained.

These analytical studies all founder on the same rock, namely, the technical problem of separating embolic fat from plasma and tissue lipids. A way to tackle this problem was shown by Hallgren *et al* (1966). Pulmonary fat emboli were dislodged by retrograde perfusion and harvested by passing the perfusate through a nylon filter of suitable pore size. A preliminary study on six dogs with bilateral femoral fractures showed that the embolic fat consisted almost entirely of triglycerides. These had a fatty acid composition unlike plasma triglycerides, but closely resembling depot fat. A difference in the fatty acid composition of triglycerides from plasma and from adipose tissue exists in man (Gelin, Hallgren, Kerstell, Rudenstam, and Svanborg, 1967) as well as in the dog (Hirsch, Farquar, Ahrens, Peterson, and Stoffel, 1960)

and it is essential that a comparable investigation be carried out on a series of necropsy cases of fat embolism.

Conclusions

The classical mechanical explanation of fat embolism has been seriously challenged but still remains valid. Marrow fat and adipose tissue are the major, if not the only, source of embolic fat, and the weight of evidence is against any significant contribution from the plasma lipids. The quantity of embolic fat required to produce clinically significant consequences in man remains uncertain; it may be in the range of 20 to 50 mg and is probably less in the presence of shock. Quantities of this magnitude are probably available at the sites of fracture and soft-tissue damage, but further studies are required. Simple extrapolations from the results of animal experiments may be seriously misleading because of species differences. Further, much work on the minimum lethal dose of fat relates to a severity and acuteness of pulmonary fat embolism which is rare in man.

Traumatic lipaemia and fat macroglobulaemia have no direct connexion with traumatic fat embolism. There is no proof, experimental or otherwise, that pulmonary fat embolism can result from a disturbance of lipid metabolism or transport. The occurrence of fat emboli with high cholesterol content is highly unusual, but has been confirmed in one instance. The application of analytical procedures to embolic lung fat in man should be pursued.

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