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FAT EMBOLISM IN KOREAN BATTLE CASUALTIES

ITS INCIDENCE, CLINICAL SIGNIFICANCE, AND PATHOLOGIC ASPECTS *

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The significance of fat embolism following trauma is controversial despite the large volume of literature on the subject. Some authors[1-4] have regarded fat embolism as a relatively common and serious complication of injury, while others[5-8] have believed that it is rarely severe enough to be of clinical importance. Surgeons who have handled large numbers of battle casualties in the Korean conflict[9,10] only exceptionally have been able to recognize the clinical syndromes described in the literature as characteristic of fat embolism. Because of such conflicting opinions, a study of this subject was begun in the Pathology Section of the 406th Medical General Laboratory. Necropsy cases of all types of trauma, including battle, were analyzed from a clinicopathologic viewpoint in an attempt to determine the specific significance of fat embolism among the many sequelae of serious injury. The present communication deals principally with 110 cases of fatal battle trauma received and reviewed at the laboratory during the year 1953. Data obtained from analysis of similar cases reviewed in 1952 and of cases of death following other types of trauma are presented whenever pertinent.

MATERIAL AND METHODS

One hundred and thirty-two cases of fatal battle trauma were studied at our laboratory in 1953. Of these, 110 were selected for investigation of the incidence, clinical aspects, and pathologic changes of fat embolism. The remaining 22 were eliminated because clinical or pathologic data were inadequate or because death occurred later than 4 weeks after injury. This arbitrary time limit for exclusion of cases was selected because in our experience fat embolism has not

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been demonstrable beyond this time. Although a few of the soldiers in the series were killed instantly or died in the chain of medical evacuation, the great majority expired at Army hospitals where necropsy facilities were available. Thus, the 110 studied were not representative of all soldiers who died of battle wounds.

Forty-four of the necropsies were done by two trained pathologists at the 11th Evacuation Hospital, to which casualties developing post-traumatic renal failure were transferred. Thirty were performed at the 46th Army Surgical Hospital by a medical officer with previous training in Pathology. The remainder were done at numerous Army surgical, evacuation, and general hospitals in Korea and Japan by various medical officers, some of whom had little pathologic experience. Clinical abstracts were available for the great majority of patients necropsied at the 11th Evacuation Hospital and the 46th Army Surgical Hospital. The available clinical data on the rest of the patients were detailed in some instances, but in others, scant.

Routine necropsy sections of tissues fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin were available for study. In occasional cases, only several sections had been prepared; in the great majority, however, there were twenty or more. In 89 cases, oil-red-O fat stains were done on frozen sections of formalin-fixed lung tissue cut at 30 to 40 μ in thickness. In 33 cases, samples of kidney, and in 24, samples of one or several portions of the brain, were stained similarly. All oil-red-O sections were graded according to their content of intravascular fat. This grading was attended by some difficulty since the fat occasionally was distributed unevenly in a section. Because it was not feasible to do large numbers of fat stains on any one organ, estimation of the amount of intravascular vacuolation in routine hematoxylin and eosin sections (in which the fat is dissolved out) was resorted to as an ancillary method of grading.

The amount of fat in the lungs was graded 0 to 8, grade 1 representing less than 10 small emboli per section and grade 8 signifying the presence of emboli in a majority of high-power fields and the appearance of extensive beading of alveolar capillaries with globules of fat. The intermediate grades are difficult to define accurately and were selected on the basis of visual impressions. Since all sections were examined at least twice and were reviewed finally within a short period, it is believed that their relative grading was reasonably accurate. In sections of lung stained with oil-red-O and in those stained with hematoxylin and eosin, grades determined independently were identical in 47 per cent of cases; they differed by one in 33 per cent, by two in 17 per cent, and by three in 3 per cent of cases. When

grades differed by one, the higher of the two was selected for statistical purposes; when by two or three, the average was chosen.

The renal content of fat was graded 0 to 8, grade 1 corresponding to less than 5 emboli per section and grade 8, to the presence of multiple emboli in the great majority of glomeruli. Hematoxylin and eosin grading was less successful in the kidneys than in the lungs. However, it was of definite value, matching the oil-red-O grading closely with few exceptions.

So few brain sections contained fat that grading was not done. Rather it was considered more appropriate to describe the occasional positive sections as having minimal, slight, or moderate quantities of fat. Recognition of fat vacuoles in hematoxylin and eosin sections of brain was difficult, so that quantification of the fat without examination of oil-red-O stains was unreliable.

Independently of the microscopic study, the abstracts of the clinical records were combed with special attention devoted to duration of life, type and distribution of wounds, presence or absence of fractures, degree of shock, and prominence of cardiovascular, pulmonary, renal, and cerebral symptoms. Other pathologic findings at necropsy, especially those referable to the cardiovascular system and lungs, were tabulated in an attempt to discover if their presence could be related statistically to the amount of fat embolism observed microscopically.

Review of the Literature

Exhaustive historical reviews of the literature on fat embolism have been written by Warthin[4] and more recently by Groskloss.[11] We shall summarize here only those aspects of the subject to which the present study may contribute pertinent information.

Etiology

By and large, there is agreement that a significant degree of fat embolism is rare except as a sequel of injury to bone or adipose tissue.[3,4,11,12] The condition has been reported in a wide variety of non-traumatic disorders,[4,11] but with few exceptions it has been mild and without clinical significance in such cases. Types of injury to bone which can result in fat embolism include gross fracture, concussion or jarring without obvious fracture, and orthopedic operations and manipulations.[4,11] The most striking examples of fat embolism following trauma to adipose tissue are cases in which victims have been beaten with resultant extensive contusion of subcutaneous tissue.[13,14] In patients dying of extensive burns, fat embolism is common, but is very rarely of significant degree.[3,15]

Pathogenesis

Most authors have accepted Gauss's[16] theory of pathogenesis of post-traumatic fat embolism. He enumerated three conditions necessary for the entrance of free fat into the circulation: (1) rupture of the envelopes of the fat cells, (2) tearing of veins, and (3) increase in pressure locally, forcing the fat into the venous system. The pressure increase can be due to hemorrhage, edema, or other factors. In bone, anatomical fixation of the veins to the walls of the haversian canals is believed to prevent their collapse and to favor the admission of fat. In opposition to the theory of Gauss was Warthin's[4] observation that the total amount of fat in embolic form often far exceeds the fat content of the injured bone. Lehman and Moore[17] offered an explanation for this apparent paradox. They claimed that part of the "embolic" fat may be produced by conversion of endogenous emulsified fat in the serum into larger droplets. Using experimental animals, they were able to effect such a conversion with various chemical agents. There is no convincing evidence that an alteration in endogenous serum fat is a factor in human fat embolism, although such a possibility has not been excluded.

Incidence

Figures on the incidence of fat embolism vary greatly depending upon the types of cases analyzed and upon whether clinical or pathologic criteria are used to make the diagnosis. Wilson and Salisbury[8] stated that in a series of 1,000 consecutive battle casualties, 8 (0.8 per cent) showed clinical evidence of fat embolism. Newman[18] reported a 6 per cent clinical incidence in 89 consecutive patients with major injuries of the long bones. Using post-mortem criteria, Robb-Smith[3] diagnosed fat embolism in 81 per cent of 115 patients who suffered fatal accidents. Of 59 medical examiner's cases in which fracture of a lower extremity occurred, Vance[12] reported fat embolism in 75 per cent. Wyatt and Khoo[19] demonstrated fat emboli in every one of 30 patients dying after injury. Nineteen necropsy cases of trauma were studied by Denman and Gragg[1]; in 9 (47 per cent) there was fat embolism. Finally, fat emboli were found[20] in 34 of 51 battle casualties who were necropsied (67 per cent); in 10 of these the amount of embolic fat was "significant."

The incidence of fat embolism found at necropsy in non-traumatic cases is generally regarded to be low. Thus Robb-Smith[3] stated that in a "large series" of non-traumatic deaths, results were negative for fat embolism except in cases of burns, in which the degree was very slight. Vance[12] found fat emboli in only 7 of 82 cases of non-traumatic deaths. In each instance, the embolism was very mild. In 15 non-

traumatic sudden deaths, Wyatt and Khoo[19] were unable to demonstrate fat emboli. Of 22 of their patients dying after a lingering illness, only one showed emboli. This patient died 3 weeks after suffering extensive burns. Denman and Gragg[1] reported a 28 per cent incidence of fat embolism in 80 non-traumatic cases selected at random. In only one of these was the degree severe.

The incidence of systemic fat embolism has not been investigated as carefully as that of the pulmonary form. Vance[12] found fat emboli in the kidneys in only a few cases of "severe and fatal pulmonary fat embolism." Sheynis,[21] who reported an 88 per cent necropsy incidence of pulmonary fat embolism in traffic accidents with bone injuries, placed the incidence of systemic fat embolism at 12 per cent. Musselman *et al.*,[22] who approached the problem clinically by analyzing the urine for free fat, discovered that 52 per cent of 109 patients suffering moderate to severe injuries had lipuria on one or more of 15 consecutive daily examinations. On the other hand, only 12 per cent of 50 patients with non-traumatic illnesses showed lipuria on one of 7 consecutive daily examinations.

Significance

The clinical significance of fat embolism is a subject on which many contradictory statements have appeared. For example, Gröndahl[6] stated that fat embolism is the cause of death in only 1 per cent of fatalities following fractures. In contrast, Warthin,[4] who encountered 9 deaths after fractures of long bones in a series of 560 necropsies, considered fat embolism the cause of death in all 9 instances. Denman and Gragg[1] considered that of their 19 necropsied patients who had suffered trauma, 6 (32 per cent) died of fat embolism. Robb-Smith[3] considered fat embolism a major cause of death in 25 per cent of 115 fatal accident cases examined at necropsy. In Vance's[12] series of 59 fatalities following fracture of a lower extremity, fat embolism was regarded as the primary cause of death in 3 (5 per cent). In 9 additional patients (15 per cent more), it was thought to be a significant factor in producing death. Musselman, Glas, and Grekin[22] concluded that fat embolism may be expected in about one half of all persons who have been either moderately or severely injured, and that about 10 per cent of patients having fat embolism will die of it.

Clinical Aspects

There is almost universal agreement in the literature that fat embolism manifests itself clinically in at least two forms: pulmonary and cerebral.[4,11,12,23] It is stated that, in the pulmonary form, evidence of respiratory distress may appear immediately following injury[4,24] or

after a free interval of hours to days. Various signs and symptoms of respiratory embarrassment have been described. These include air-hunger, dyspnea, cyanosis, chest pain, cough, expectoration of thin mucoid sputum which may be blood-streaked, tachypnea, pulmonary edema, and râles. In some cases it is believed that the respiratory involvement is sufficiently extensive to cause death.

A syndrome of cerebral fat embolism more clear cut than the respiratory one has been described repeatedly in the literature. After a characteristic free interval of hours to days (3 to 6 days is said to be the average time[11]), the patient exhibits mental changes—insomnia or somnolence, apathy, amnesia, disorientation, delirium, stupor, and, finally, coma. A wide variety of neurologic disturbances, including paralysis, spasm, convulsions, rigidity, and reflex changes, may accompany the mental aberrations. One reported manifestation of cerebral fat embolism is failure to recover consciousness after operative anesthesia.[18] It has been stated that signs of increased intracranial pressure are almost always absent, and that the cerebrospinal fluid is normal in nearly every case.[25] Most of the reported cases of cerebral fat embolism have been fatal; however, recovery of patients with suggestive manifestations has been recorded a few times.[25,26] The cerebral form of fat embolism may or may not be preceded by respiratory signs or symptoms.[27]

Early authors[4] described, in addition to respiratory and cerebral forms, a cardiac syndrome for fat embolism characterized by precordial pain, a rapid, irregular heart rate, increasing venous pressure, and falling arterial pressure. Most modern writers, however, do not recognize the cardiac symptom complex.

Other signs of systemic fat embolism include: (1) the presence of free fat in the urine (this may be detected as early as the first day after injury[22]); (2) the appearance of crops of skin petechiae, most common on the neck, shoulders, and chest; and (3) the presence of intravascular fat globules[28] and perivascular edema and hemorrhage[29] in the eyegrounds. A final manifestation of fat embolism is an alteration of body temperature. In the typical case this is said to reach 103° F. at the height of the disease and to rise even higher terminally.[30]

Pathologic Features

Pathologic changes due to fat embolism are encountered most commonly in the lungs,[11] which have been described as heavy and voluminous, with edema and patchy areas of emphysema. The pleural surfaces are stated to exhibit focal hemorrhages on a pink-gray background. The pulmonary arteries or veins may contain grossly visible fat. Micro-

scopically, the vessels, primarily arterial and capillary, are occupied and often distended by round, oval, dendritic, or stellate fat globules. When the fat droplets are numerous in the capillaries of the alveolar walls, these often have a beaded appearance. In a small number of cases bone marrow emboli also are found in the arterial lumina.[4] The alveoli may contain edema fluid, blood, and, in some instances, globules of fat.[23] The fat may be free or phagocytized by mononuclear or foreign body giant cells.[23]

Although emboli have been observed in almost every organ and tissue of the body when the fat has entered the systemic circulation, the pathologic changes in the systemic form of fat embolism are most intense in the brain, kidneys, and heart.[4,11] The brain characteristically shows crops of emboli in capillaries and arterioles of both gray and white matter. In severe cases, there are multiple petechiae and small areas of softening which are most numerous in the white matter of the cortex. The gray matter, with its richer blood supply, is much less vulnerable to necrosis.[12] Microscopically, one encounters small hemorrhagic and anemic infarcts often surrounding arterioles plugged with fat. The hemorrhagic infarct appears characteristically as an area of anemic necrosis surrounded by a ring of extravasated blood. The infarcts may excite an inflammatory response and finally evolve into glial scars.[25]

The kidneys show no gross changes. Microscopically, emboli are found chiefly in the glomerular capillaries, to a lesser extent in the intertubular vessels, and occasionally within the tubular lumina. When fat is abundant in the glomeruli, it forms characteristic pretzel-shaped masses. Necrotic or degenerative changes in the renal parenchyma secondary to fat embolism apparently do not occur.

The heart has been described by various authors[3,4,11] as showing right-sided dilatation in cases of pulmonary fat embolism. Where systemic embolism has involved the cardiac capillaries, the myocardium is said to exhibit small hemorrhages and areas of yellowish degeneration surrounded by hemorrhage.[4] Microscopically, fatty degeneration of the muscle fibers surrounding the emboli, hemorrhages, and anemic infarcts have been described.[4]

Results of Analysis

Clinical Data

The ages of the patients ranged from 18 to 32 years. The average age was 22; less than 10 per cent were over 25 years. Eighty-five per cent of the injured men were wounded by shell fragments; 15 per cent, by bullets. Ninety per cent of the shell fragment wounds and 33 per

cent of the bullet wounds were multiple. Three fourths of the patients had fractures. In a few instances, significant burns complicated the injuries. The anatomical distribution of the wounds is presented in Table I.

The duration of life after wounding ranged from seconds to 28 days. Approximately one fourth of the patients expired in less than 24 hours;

TABLE I

Distribution of Wounds: 110 Cases

Location	Number of cases
Head and neck	4
Trunk	22
Mixed, excluding extremities	5
Extremities	20
Mixed, including extremities	59

two fifths survived between 1 day and 1 week; and one third died later than 1 week after wounding.

Incidence

Of the 89 patients from whom oil-red-O sections of lung were examined, 83 (93 per cent) showed pulmonary fat emboli. Using intravascular vacuolation in routine hematoxylin and eosin sections as the sole criterion for fat embolism, findings were positive in 87 of 110 cases, an incidence of 79 per cent. It is apparent, then, that minimal degrees of embolism occasionally escaped detection without the use of fat stains. Analysis of both routine and fat stains, as outlined in Material and Methods, revealed that 19 per cent of the soldiers showed moderate to marked degrees of pulmonary fat embolism (grades 5 to 7); 31 per cent showed slight degrees (grades 3 and 4); and 50 per cent showed minimal degrees or none at all (grades 0 to 2).

Table II shows the relation of pulmonary fat embolism to the time of death after wounding.

The more severe degrees of pulmonary fat embolism were seen most often in soldiers dying during the first week after wounding. The peak incidence was in the early part of the week after the first day. There was a definite tendency for the pulmonary fat content to be less during the second, third, and fourth weeks. We have seen fat embolism in soldiers who presumably lived no longer than a few minutes as well as in one who survived 24 days after injury.

Extensive experience with both routine and fat stains has shown that systemic fat emboli are most abundant and easiest to recognize

microscopically in the kidneys. For this reason, the presence of fat in renal vessels has been regarded as the most sensitive pathologic index of the entrance of emboli into the systemic circulation. Previous studies of workers at this laboratory[14,31] and of others[12] have revealed that (1) renal involvement rises in incidence and grade with increasing degrees of pulmonary fat embolism, and (2) minimal to slight

TABLE II

Relation of Fat Embolism to Duration of Life after Wounding

	0-1 day	1+-4 days	4+-7 days	7+-14 days	14+-30 days
Number of cases	26	24	22	26	9
Average grade	2.5	3.4	2.9	2.2	2.0
Percentage of cases, moderate to marked	19	33	23	12	0

degrees (grades 0 to 4) of the latter are only rarely accompanied by the appearance of fat in the kidneys. For these reasons, in the present series, renal fat stains were done routinely only in cases in which the grade of pulmonary fat embolism was 4 or higher. In 26 such instances, the kidneys were positive in 17. In the remaining cases, in which the grade of pulmonary fat embolism was 3 or less, and in which hematoxylin and eosin sections of the kidneys disclosed no evidence of fat embolism, it was considered justifiable and conservative to grade the renal fat embolism as "none to minimal" (grades 0 to 2). Combining the results of grading both routine and fat stains, it was found that of the 110 patients, 92 per cent showed minimal or no renal fat embolism. Four per cent exhibited slight (grades 3 and 4), and an additional 4 per cent, moderate to marked degrees (grades 5 to 7).

Because of the importance of cerebral fat embolism as a potential cause of death, sections of the central nervous system were studied with fat stains whenever the pulmonary grade was 4 or greater, and brain tissue was available. Usually one section of cortex was examined. Often additional sections from cortex and other parts of the brain were studied as well. In the 24 cases in which the brain was stained with oil-red-O, findings were positive in 5. Cerebral fat embolism was less common and almost always less marked in degree than renal fat embolism. Thus, of the 24 cases mentioned, the kidney was positive for fat in 15, an incidence three times that of the brain. Similarly, in a previous series dealing with various types of trauma,[14] of 42 cases in which both renal and cerebral fat stains were done, the kidney was positive for emboli in 18 and the brain in only 9. In no case, in either the present or the previous series, was the brain posi-

tive when the kidney was negative. In the present series, in 3 of 4 cases in which renal fat embolism was slight, cerebral embolism was minimal in 2 and absent in the third (in the fourth case no oil-red-O section of brain was available). In 3 of 4 cases in which renal fat embolism was moderate to marked, brain embolism was minimal in 2 and moderate in the third (in the fourth case no oil-red-O section of brain was available).

In summary, about 90 per cent of soldiers dying in hospitals less than 1 month after battle trauma showed pulmonary fat embolism at necropsy; however, only 19 per cent showed more than a slight degree. Less than 10 per cent of the soldiers had more than minimal renal fat embolism, and much fewer had more than minimal cerebral involvement.

With regard to the comparative incidence and severity of fat embolism in various types of trauma, our experience has been that the highest incidence and most severe grades have been observed in individuals who have been severely beaten and who had extensive contusions of the extremities. We have seen 13 such cases. A study of over 50 deaths following vehicular accidents has revealed an incidence and severity of fat embolism roughly paralleling that complicating battle trauma. The lowest incidence and mildest degrees of pulmonary fat embolism among the large groups of traumatic cases studied have been in patients who have died of single bullet wounds of the head or chest (over 40 cases examined).

Although we have not made an organized study of the incidence of pulmonary fat embolism in non-traumatic cases, we have been impressed with both its rarity and its mildness whenever present.

In 18 patients dying after extensive burns, we have found absent or minimal pulmonary fat embolism in 15, slight embolism in 2, and moderate embolism in one.

Pathogenesis

Little new information on the pathogenesis of fat embolism was obtained from an analysis of the present series of cases. It was not possible to estimate accurately from the necropsy records the amounts of injury to soft tissues and bone, so these could not be related to the degree of pulmonary fat embolism. However, it was feasible to make a correlation between the topography of the wounds, the presence or absence of fractures, and the amount of fat in the lungs. Thus, it was found that of 31 patients having wounds confined to the head, neck, trunk, or a combination of these, only one showed moderate pulmonary fat embolism. In contrast, of 79 patients whose extremities were

involved, 20 showed moderate to marked fat embolism. One explanation for this difference probably depends upon the greater amount of osseous damage suffered in the 79 cases involving the extremities. Of the latter, 63 were associated with fractures and 19 of these showed moderate to marked pulmonary fat embolism. On the other hand, only one of the 16 patients without accompanying fractures exhibited moderate embolism. Although the wounded-in-action cases provided no opportunity for correlation between the amount of soft tissue damage and the degree of fat embolism, study of our 13 cases in which death was due to beating suggested the importance of trauma to adipose tissue in the production of fat embolism. These patients at necropsy commonly showed marked pulmonary, and occasionally marked systemic fat embolism despite the absence of obvious fractures. It is possible, of course, that jarring of the long bones with microscopic fractures provided a source of embolic fat in these cases.

Clinical Aspects

An attempt to delineate a pulmonary symptom-complex in the present series of cases was unsuccessful. Dyspnea and cyanosis often were mentioned as prominent features in the courses of these patients. However, there appeared to be no correlation between these symptoms and the amount of fat in the lungs. Admittedly, a rare patient had at some interval after wounding a more or less acute onset of respiratory distress, and died, showing moderate to marked pulmonary fat embolism. On the other hand, such histories were obtained also in association with only minor degrees of embolism, and usually were absent in cases showing high grades.

Likewise there was no evidence in this series to support a cardiovascular symptom-complex. No signs of right-sided heart failure which could be correlated with moderate or marked pulmonary fat embolism were observed. In a small percentage of the cases, in which it was possible to estimate the degree of shock, no correlation was demonstrable between it and the pulmonary fat content. Furthermore, the occasional occurrence of unexpected sudden death bore no consistent relationship to the quantity of embolic fat in the lungs.

With reference to systemic fat embolism, ophthalmoscopic examinations and laboratory examinations of the urine for fat were not recorded in our abstracts. Cutaneous petechiae were noted in occasional cases, but could not be correlated statistically with the degree of fat embolism at necropsy.

Only two patients presented a clinical picture suggestive of cerebral fat embolism. At necropsy, one had a moderate degree, while the other

showed cerebral edema, but no fat embolism. The former (case 1) was a 29-year-old soldier who sustained many shell fragment wounds of the extremities causing numerous fractures. Twenty-four hours after extensive débridement and multiple amputations, he became stuporous and hypertensive. Cranial exploration revealed the brain to be under considerable pressure, but there was no hemorrhage. The patient expired 10 hours after his second operation (approximately 52 hours after wounding).

In our 1952 series of soldiers dying after battle wounds,[14] there was a similar incidence of clinically apparent cerebral fat embolism (1 of 109 patients). This one patient (case 2), who sustained many wounds from a land mine explosion, lapsed into deep coma following a leg amputation and extensive débridement of wounds. Pupillary signs, generalized convulsions, and hypertension appeared 49 hours post-operatively. Cranial exploration gave negative findings. Skin petechiae appeared and the patient died 55 hours after his original operation (63 hours after wounding).

Pathologic Features

We have been unable to find any characteristic gross pathologic changes in lungs showing fat embolism. There was no edema, focal hemorrhage, patchy emphysema, or atelectasis described consistently in the lungs with the more severe grades of embolism. Table III shows the average combined weights of 102 pairs of lungs correlated with

TABLE III

Average Combined Weights of the Lungs in Fat Embolism

Grade of embolism	Time of death			
	Under 1 day	1–2.5 days	2.5–5 days	Over 5 days
	gm.	*gm.*	*gm.*	*gm.*
0–2	1246 (12 cases)	963 (4)	1300 (8)	1171 (29)
3–4	1404 (7)	1020 (2)	1064 (8)	1135 (14)
5–7	871 (5)	931 (4)	1235 (3)	1058 (6)

the grades of fat embolism at various times at which death occurred following wounding. These data afford no support for the thesis that fat embolism favors the development of pulmonary edema.

After considerable experience it became possible to recognize with ease the vacuoles produced by fat emboli in hematoxylin and eosin sections of the lung. In the larger vessels these appeared as large,

round or oval spaces which often coalesced (Fig. 1). Unlike artifactitious spaces, which merely displaced intravascular red cells, the vacuoles of fat compressed them so that their surfaces became concave along the margins of the vacuoles. Arterioles and capillaries were plugged and distended by round, oval, or reniform vacuoles. At the periphery the vessel walls and their endothelial linings were tightly compressed, suggesting great tension (Fig. 1). In sections of tissues fixed in acid formalin the deposition of delicate, golden-yellow crystals of formalin pigment in the vacuoles was of confirmatory value in identifying them as fat. The use of fat stains revealed a striking picture often outlining the pulmonary arterial tree and capillaries of the alveolar walls (Fig. 2).

In 4 of our 110 cases bone marrow emboli were found in small numbers in the pulmonary arteries (Fig. 3). In one case a tiny fragment of embolic skin was seen. Commonly, thrombi composed largely of fibrin and eventually penetrated by endothelial cells lay in juxtaposition to the embolic fat globules. Since these thrombi, more often than not, were situated away from the fat emboli, it seemed probable that the association of the two was of a collision type.

Microscopically, just as grossly, we were unable to correlate the presence of pulmonary fat emboli with focal edema, hemorrhage, emphysema, or atelectasis.

The presence of fat droplets within the alveoli was unusual. Occasionally, they were extravasated with blood. In one case there was focal massive outpouring of fat into the air spaces in the absence of obvious hemorrhage. Phagocytosis of extravasated fat by alveolar phagocytes was not observed. The lipochrome granules, so commonly seen in these cells, stained orange or rust color with oil-red-O in contrast to the bright red of the embolic fat. Likewise, the quantity of phagocytes bore no consistent relationship to the amount of fat within nearby vessels. In only one case was there a reaction of vascular endothelium to fat emboli. In it the endothelial cells surrounding the fat were filled with numerous, small, uniform vacuoles, presumably fatty. No variation in the appearance of the emboli was detected in relation to time. The fat seen in several cases in which death occurred less than 10 hours after wounding appeared identical to that observed within pulmonary vessels as late as 24 days after injury.

No clues were apparent from the histologic sections of lung as to how the embolic fat was eliminated. It is possible that local enzyme activity is responsible for the gradual elimination of the pulmonary fat or that the droplets are continually being propelled into the systemic circulation and excreted by the kidneys. The failure to find fat

regularly in the air spaces does not exclude the possibility of rapid elimination in the sputum.

The topographic localization of fat emboli within the lungs was not worked out in detail. Generally, sections taken from various regions of the lungs contained fairly similar amounts of fat. Occasionally, one section differed by two grades from another, and rarely, by three. In sections in which only a small amount of fat was present, it often was confined to a thin rim of lung beneath the pleural surface.

When more than minimal, renal fat embolism usually was easy to recognize in hematoxylin and eosin sections by observing the vacuolation of capillaries of the glomerular tuft (Fig. 4). When the degree of embolism was minor, the fat was most likely to appear in the glomeruli near the renal capsule. Emboli were seen also in the intertubular vessels, chiefly in the cortex (Fig. 5). Rarely, fat in the form of droplets or casts was visible within the tubules (Fig. 6). In a single case of death due to beating, fibrin thrombi lay in juxtaposition to the fat emboli in the glomeruli. Fat emboli were seen in the kidneys as early as 10 to 18 hours after wounding and as late as 17 days.

In the central nervous system, emboli scattered in groups were seen in both gray and white matter. Vacuolation in hematoxylin and eosin sections of brain often was difficult to recognize. Occasionally, an empty dilated vessel with a tenuous wall was highly suggestive of fat embolism (Fig. 7). In only 2 cases, cases 1 and 2, have we observed parenchymal lesions secondary to the emboli. In those, petechiae and small areas of anemic necrosis (Fig. 8) appeared, especially in the white matter of the cortex, but elsewhere as well. The infarcts were characterized by loosening and loss of tinctorial properties of the intercellular framework, and shrinkage of both nerve and glial cells. Affinity for both eosin and fat stains was decreased. Some lesions showed infiltration by polymorphonuclear leukocytes. In occasional infarcts, centrally situated capillaries or arterioles were plugged with fat. Using fat stains, emboli were seen most commonly in the gray matter of the cortex (Fig. 9). A confusing element in the interpretation of fat stains of the brain was the frequent presence, in a perivascular location, of phagocytes containing lipochrome granules. These granules, which had a golden color in hematoxylin and eosin sections, seemed to be entirely unrelated to fat emboli, ofter appearing in their absence.

Oil-red-O stains were done on only a few heart sections. In case 1, small groups of capillaries were distended with fat globules (Fig. 10). The myocardium showed a few, scattered, small foci of degeneration, characterized by hyalinization of sarcoplasm and nuclear pyknosis. It

was not certain that these changes were ante mortem. Neither fatty degeneration of muscle fibers surrounding the emboli nor petechiae were observed.

Next to the lungs and kidneys, fat emboli were recognized most easily in hematoxylin and eosin sections of the adrenal glands and spleen. There they produced characteristic round, oval, and sausage-shaped vacuoles which were most numerous in the subcapsular zones (Figs. 11 and 12). In occasional cases, vacuoles highly suggestive of fat emboli were seen in other organs. With the exception of the brain, we have not seen degenerative parenchymal lesions secondary to fat embolism.

Discussion

Because of the many variables existing in any large series of traumatic cases, our high incidence of fat embolism (about 90 per cent) cannot be compared reasonably with incidences in most other reported series. Mallory's[20] collection of necropsies on World War II wounded is perhaps as close in nature to ours as any in the literature. His incidence of pulmonary fat embolism (67 per cent) is lower than ours. However, his figure for "significant" embolism (20 per cent) tallies closely with ours for moderate to marked embolism (19 per cent). Likewise, our incidence of moderate to marked systemic fat embolism (4 per cent) is identical to that given by Mallory for "significant" systemic fat embolism.

The major disagreement we have with the widely accepted concept of fat embolism as a clinicopathologic entity is in regard to its rôle in producing significant pulmonary dysfunction. Analysis of our cases did not reveal statistical evidence that fat embolism causes pulmonary distress. Likewise, there was no pathologic correlation between the amount of pulmonary fat embolism observed and the presence and degree of pulmonary edema, pulmonary hemorrhage, atelectasis, emphysema, or right-sided cardiac dilatation. Mallory[20] was similarly unable to correlate fat embolism and pulmonary edema on a statistical basis. While such evidence cannot exclude the possibility that serious pulmonary embarrassment may result from embolic fat in occasional cases, such cases must be quite uncommon, if they exist at all, in order to escape detection in such a large series as the present one.

In reviewing the literature on fat embolism, we have been impressed by the lack of "controls," i.e., injured patients who died showing no, or at most slight, fat embolism at necropsy. Failure to compare such cases with cases of moderate to marked fat embolism exposes one to the risk of fallacious reasoning in implicating fat embolism as the cause of various clinical and pathologic findings. Again, the frequent

absence of pulmonary symptoms and signs antedating the onset of cerebral fat embolism[11,25,29] is difficult to explain if one holds that pulmonary fat embolism produces respiratory embarrassment. Cerebral fat embolism is, with possible rare exceptions, encountered only when the degree of pulmonary involvement is moderate to severe.

Our conclusions, based on clinical data, are similar to those of Armin and Grant,[32] who employed experimental methods. These authors produced pulmonary fat embolism by injecting rabbit perirenal fat into ear veins of unanesthetized rabbits. They estimated the amount of fat which it was necessary to inject in order to produce a degree of pulmonary fat embolism equivalent to a severe degree in the human. This estimate was based on measurement of the extractable fat content of severely involved human and rabbit lungs, as well as on grading of histologic sections. Their conclusions were: (1) The production of pulmonary fat embolism corresponding to a severe grade in the human caused no change in blood pressure, pulse rate, or respiration in the normal rabbit. The dose given to produce such embolism was much less than that required to kill the rabbit. (2) In animals subjected to severe hemorrhage (averaging about 40 per cent of the blood volume) the additional production of severe pulmonary fat embolism did not alter the clinical picture or increase the mortality above that due to hemorrhage alone. (3) The production of severe pulmonary fat embolism had no effect on the response of the animals to transfusion after hemorrhage. (4) Unless the rabbit tolerates fat embolism better than man, human gross pulmonary fat embolism is unlikely to provoke symptoms or to be alone or in part responsible for death after injury.

As a corollary to our inability to relate evidence of pulmonary distress to fat embolism, our mortality rate (i.e., the percentage of our traumatic deaths attributable to fat embolism) is exceedingly low (about 1 per cent) as compared with rates given elsewhere in the literature. We have considered as proved fatal cases only those in which death was associated with a typical cerebral syndrome clinically and a significant degree of cerebral fat embolism pathologically. The high mortality rates given in the literature depend largely upon the assumption that moderate to severe grades of pulmonary fat embolism, whenever demonstrated, represent a primary cause of death or contribute to death as a major factor. Since we have been unable to correlate pulmonary dysfunction with fat embolism, we must consider this assumption to be gratuitous.

Several objections may be raised to the nature of the material from

which we have drawn our conclusions. (1) The clinical abstracts at our disposal were not invariably detailed. (2) Field surgeons caring for large numbers of wounded soldiers, most of them seriously ill, may not have recorded accurately or uniformly any but the more severe signs or symptoms. (3) Pathologically, we were unable to judge the ages of pulmonary fat emboli; that is, we could not determine whether the emboli had accumulated in successive crops over a period of time or had involved the lungs in a single massive onslaught. Such a determination, if possible, would undoubtedly have increased the value of our clinicopathologic correlation. Despite these objections (one or more of which apply equally well to other series in the literature), we think that: (1) Little in the way of conclusive proof has been offered for the opinion that moderate to severe pulmonary fat embolism causes significant pulmonary dysfunction or death; (2) other possible sequelae of injury have not been excluded adequately as causative agents of pulmonary signs and symptoms when such do appear.

With regard to cerebral fat embolism, we have been impressed with the rarity with which it is present in significant amounts (1 per cent of necropsied cases of battle trauma).

Conclusions

A clinicopathologic analysis of 110 cases of death occurring at military hospitals up to 4 weeks after battle trauma was made to determine the incidence and significance of fat embolism.

Fat embolism, as evidenced by the presence of fat droplets in the pulmonary vessels, was demonstrable in approximately 90 per cent of the 110 patients. In only 19 per cent was the degree of pulmonary fat embolism more than slight.

Of the 110 patients, only 4 per cent showed more than slight systemic fat embolism, as evidenced by the appearance of fat in the kidneys, and only 1 per cent showed fatal (cerebral) fat embolism.

From both clinical and pathologic viewpoints, there was no evidence from the analysis that fat in the lungs causes pulmonary dysfunction or death. This finding is at marked variance with the concept of the significance of pulmonary fat embolism accepted in the literature.

Fat emboli may be recognized and quantified with considerable accuracy without the use of fat stains by searching for and estimating the amount of intravascular vacuolation. This can be done with greatest success in the lungs, and with somewhat less success in the kidneys.

It is possible that detailed clinical and laboratory investigation of

injured patients may uncover a significance of fat embolism which is hidden by the more obtrusive complications of trauma in a routine clinical investigation.

I acknowledge the contributions of all medical officers who cared for the soldiers forming the basis of this investigation. Special gratitude is due Maj. John Lukeman, who initiated the study; 1st Lt. Joseph Strawitz and Capt. William Blake, who performed many of the necropsies; and members of the Surgical Research Team, who studied many of the patients clinically.

REFERENCES

1. Denman, F. R., and Gragg, L. Fat embolism: a diagnostic enigma. *Arch. Surg.*, 1948, **57**, 325–332.
2. Glas, W. W.; Grekin, T. D., and Musselman, M. M. Fat embolism. *Am. J. Surg.*, 1953, **85**, 363–369.
3. Robb-Smith, A. H. T. Pulmonary fat-embolism. *Lancet*, 1941, **1**, 135–141.
4. Warthin, A. S. Traumatic lipaemia and fatty embolism. *Internat. Clin.*, 1913, s. 23, **4**, 171–227.
5. Darrach, W. Discussion of: Harris, R. I.; Perrett, T. S., and MacLachlin, A. Fat embolism. *Ann. Surg.*, 1939, **110**, 1113–1114.
6. Gröndahl, N. B. Untersuchungen über Fettembolie. *Deutsche Ztschr. f. Chir.*, 1911, **111**, 56–124. (Cited by Scuderi.[30])
7. Whitson, R. O. A critique of fat embolism. *J. Bone & Joint Surg.*, 1951, **33-A**, 447–450.
8. Wilson, J. V., and Salisbury, C. V. Fat embolism in war surgery. *Brit. J. Surg.*, 1943–44, **31**, 384–392.
9. Artz, C. P. Personal communication.
10. Howard, J. M. Personal communication.
11. Groskloss, H. H. Fat embolism. *Yale J. Biol. & Med.*, 1935–36, **8**, 59–91, 175–197, 297–315.
12. Vance, B. M. The significance of fat embolism. *Arch. Surg.*, 1931, **23**, 426–465.
13. Bürger, L. Die Fettembolie und ihre Bedeutung als Todes-und-Krankheitsursache. *Vrtljschr. f. gerichtl. Med.*, 1910, **39**, Suppl., 159–172. (Cited by Vance.[12])
14. Scully, R. E. Fat embolism. In: Annual Historical Report, 406th Medical General Laboratory, 1952, pp. 197–201.
15. Gröndahl, N. B. Cited by Groskloss.[11]
16. Gauss, H. The pathology of fat embolism. *Arch. Surg.*, 1924, **9**, 592–605. (Cited by Vance.[12])
17. Lehman, E. P., and Moore, R. M. Fat embolism, including experimental production without trauma. *Arch. Surg.*, 1927, **14**, 621–662.
18. Newman, P. H. The clinical diagnosis of fat embolism. *J. Bone & Joint Surg.*, 1948, **30-B**, 290–297.
19. Wyatt, J. P., and Khoo, P. Fat embolism in trauma. *Am. J. Clin. Path.*, 1950, **20**, 637–640.
20. [Mallory, T. B.] General Pathology of Traumatic Shock. In: The Physiologic Effects of Wounds, by the Board for the Study of the Severely Wounded. North African-Mediterranean Theater of Operations. Office of the Surgeon General, Department of the Army, Washington, D.C., 1952, pp. 283–305.

21. Sheynis, M. I. Ukranian Inst. for Orthop. and Traumatol., Kieff. [Traumatic fat embolism.] *Arkh. Patol.*, 1951, **13**, Pt. 4, 103–104. (Abstracted in Excerpta Medica, General Path. & Path. Anat., 1952, **5**, 517.)

22. Musselman, M. M.; Glas, W. W., and Grekin, T. D. Fat embolism, a clinical investigation. *A. M. A. Arch. Surg.*, 1952, **65**, 551–556.

23. Warren, S. Fat embolism. *Am. J. Path.*, 1946, **22**, 69–87.

24. Bürger, L. Die Bedeutung der Fettembolie für den Kriegschirurgen. *Med. Klin.*, 1915, **11**, 996–1001. (Cited by Warren.[23])

25. Winkelman, N. W. Cerebral fat embolism; a clinicopathologic study of two cases. *Arch. Neurol. & Psychiat.*, 1942, **47**, 57–76.

26. James, E. S. Fat embolism. *Canad. M. A. J.*, 1950, **62**, 548–550.

27. Strauss, H. Cerebrale Fettembolie. *Zentralbl. f. d. ges. Neurol. u. Psychiat.*, 1933, **66**, 385–400. (Cited by Groskloss.[11])

28. Oppenheimer, H. Multiple Fettembolien des grossen Kreislaufs. *Klin. Wchnschr.*, 1929, **24**, 25. (Cited by Newman.[18])

29. McArdle, M. J. F. Personal communication. (Cited by Newman.[18])

30. Scuderi, C. S. Fat embolism, a clinical and experimental study. *Surg., Gynec. & Obst.*, 1941, **72**, 732–746.

31. Lukeman, J. Fat embolism. In: Annual Historical Report, 406th Medical General Laboratory, 1951, pp. 92–94.

32. Armin, J., and Grant, R. T. Observations on gross pulmonary fat embolism in man and the rabbit. *Clin. Sc.*, 1951, **10**, 441–469.

[*Illustrations follow*]

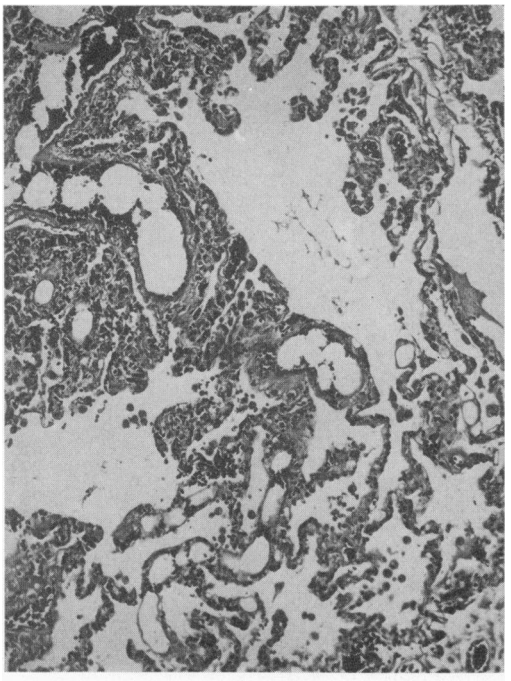
LEGENDS FOR FIGURES

FIG. 1. Lung. The arteries contain multiple round and oval vacuoles. Several capillaries of the alveolar walls are distended by large vacuoles. Hematoxylin and eosin stain. × 110.

FIG. 2. Lung. Arteries and capillaries of the alveolar walls are plugged with fat. The alveolar walls present a beaded appearance. Oil-red-O stain. × 100.

FIG. 3. Lung. Bone marrow embolus in artery. Hematoxylin and eosin stain. × 200.

FIG. 4. Kidney. Many capillaries of the glomerular tufts are distended by fat vacuoles. Hematoxylin and eosin stain. × 100.



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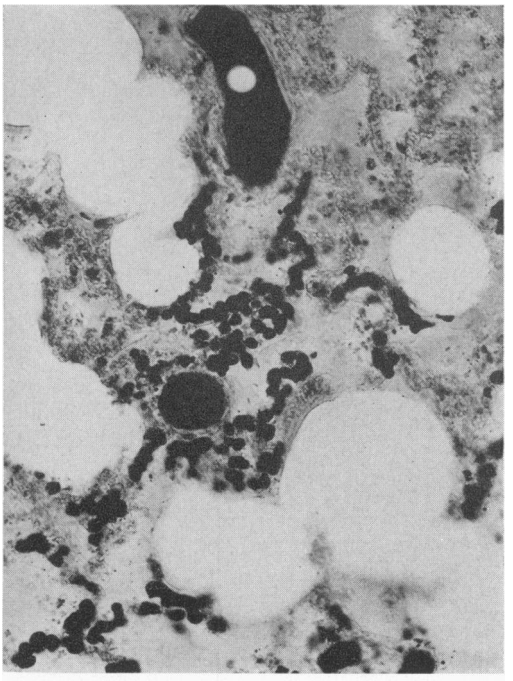

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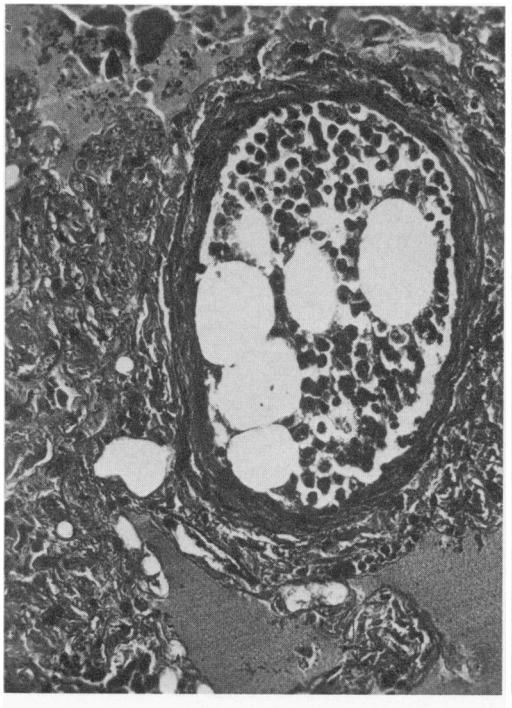

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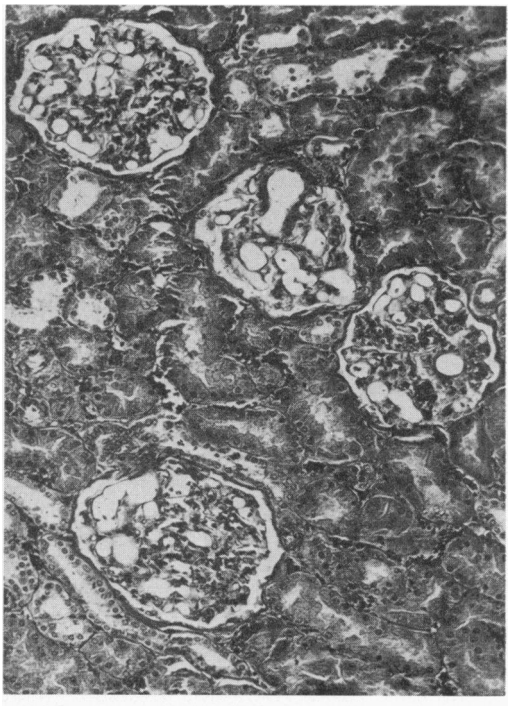

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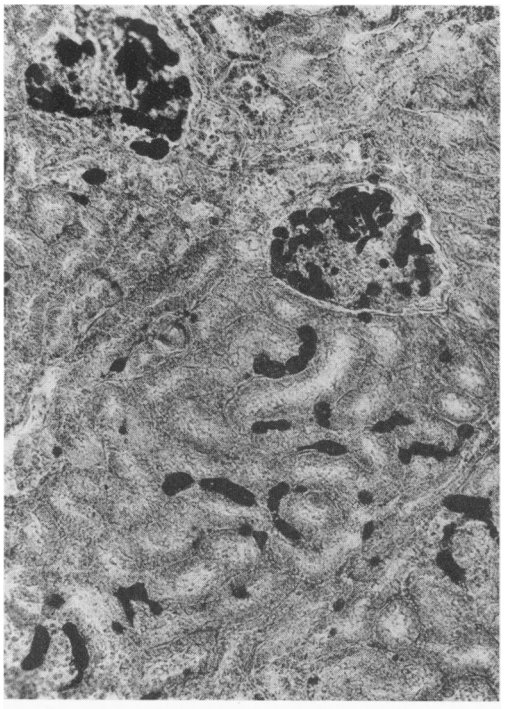
FIG. 5. Kidney. The glomeruli contain pretzel-like masses of fat. The intertubular vessels also are plugged with fat. Oil-red-O stain. × 100.

FIG. 6. Kidney. The uniformly black intratubular casts are fat. The paler granular casts are of hemoglobin type. Oil-red-O stain. × 100.

FIG. 7. Posterior pituitary lobe. Three small vessels are distended by vacuoles suggestive of fat. Hematoxylin and eosin stain. × 650.

FIG. 8. Cerebral cortex. A pale, irregular area of rarefaction is seen at the junction of gray and white matter. Oil-red-O stain. × 50.



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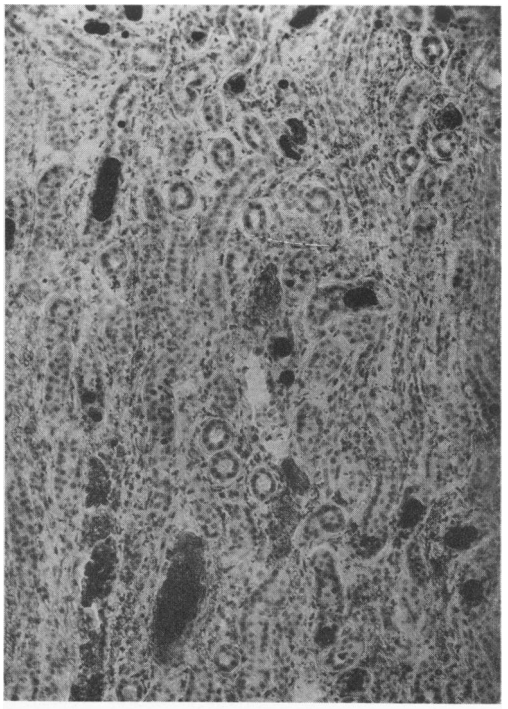

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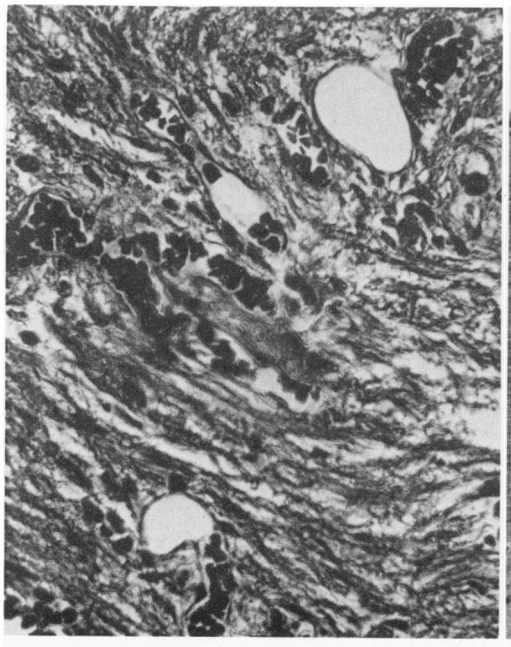

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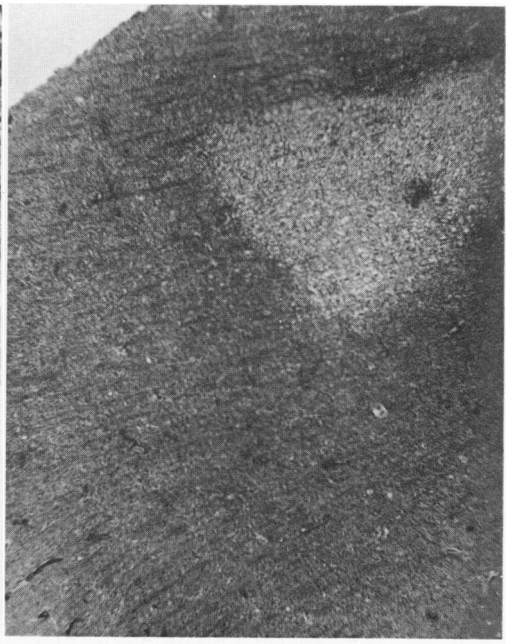

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FIG. 9. Cerebral cortex. The gray matter contains numerous fat emboli. Oil-red-O stain. × 100.

FIG. 10. Myocardium. A group of capillaries contain fat emboli. Oil-red-O stain. × 108.

FIG. 11. Adrenal cortex. Many sinusoids are distended by round and sausage-shaped vacuoles produced by fat emboli. Hematoxylin and eosin stain. × 138.

FIG. 12. Spleen. Several arterioles are distended by vacuoles of fat. Hematoxylin and eosin stain. × 100.

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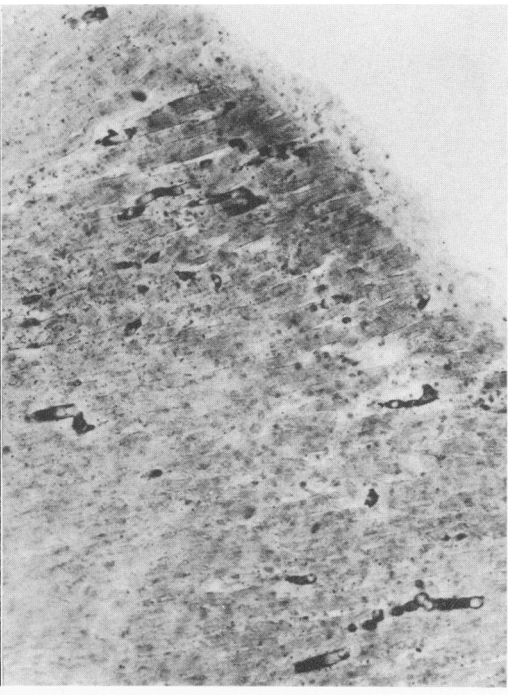

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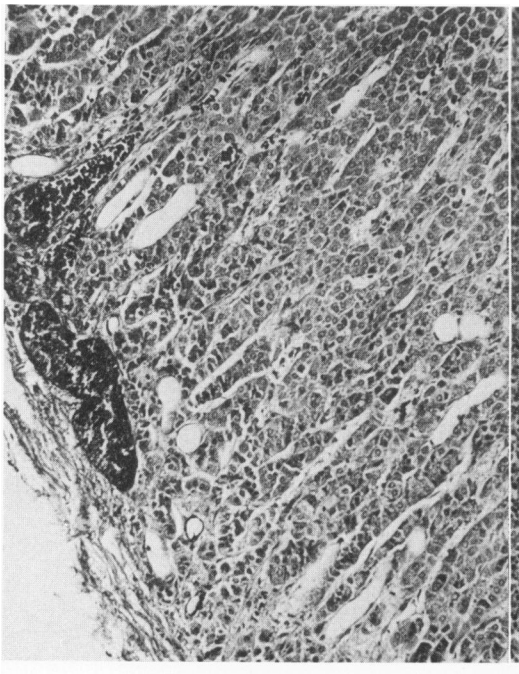

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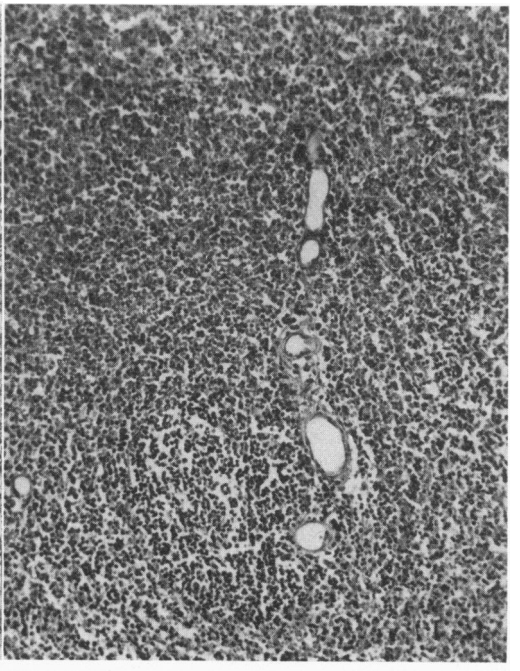

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