PARKLAND MEMORIAL HOSPITAL

MEDICAL GRAND ROUNDS

January 25, 1968

LIPID EMBOLIZATION

Case #1: TRAUMATIC FAT EMBOLI ([redacted])

The patient was a 21 year old [redacted] female who on [redacted] 1967 was riding her Honda motorcycle at approximately 40 miles per hour when a car traveling in the opposite direction made a left turn in front of her. She swerved, receiving a glancing blow to the right lower leg and on admission to [redacted] was found to have a comminuted fracture of the right femur and an apparent fracture of the tip of the right lateral maleolus. She was at no time unconscious and was alert both before and after open reduction of the femural fracture. She continued to make an uneventful recovery until the afternoon of [redacted] four days after the accident, at which time she suddenly became dyspneic with a respiratory rate estimated at 80, tachycardia of 150, and a temperature of 104°. She was mildly confused and at this time occasional petechia were noted on the chest. A chest x-ray at that time was suggestive of acute pulmonary edema. The patient was given oxygen and digitalized. A diagnosis of fat embolism was suspected; however, no fat could be detected in the urine by Sudan III stain. By the following day the patient had become obviously anoxic and remained desaturated despite tracheostomy and IPPB with 100% oxygen.

She was therefore transferred to [redacted] where rectal temperature was 104°, pulse 120, respiration 40. The patient was noted to be cyanotic but alert. The petechia were again noted on the chest. Lungs were clear. Hemoglobin on admission was 13.8, white count 2100; 10-15 red cells, and 30-40 white cells were noted in the urine. BUN was 11, CO_2 combining power 27 mEq/liter, pH 7.35, CO_2 tension 54; PO_2 was markedly low at 25, and oxygen saturation was 44%. Serum lipase was 0.96 ml/n/NaOH (normal - 0.5-1.5). The patient was treated with 100% O_2 IPPB and sedation. Though she remained alert, she continued to be cyanotic, with a PO_2 of 130-200 on 100% oxygen. Oliguria was noted at the time of admission and by the second day she was virtually anuric. Guaiac positive stools were also present. By 9/13/67 the BUN was 54, sodium was 127, potassium 4.4, pH 7.45, PCO_2 32, and PO_2 200 on 100% O_2. On the 4th hospital day, 10 days after the initial accident, the patient developed progressively severe respiratory stress, became increasingly cyanotic, developed anxiety and disorientation, and died three and one-half hours later.

At autopsy numerous fat emboli were demonstrated on Sudan III stain throughout the lungs, heart and kidney. Considerable hemorrhage was noted in the alveoli. The kidneys showed acute infarcts with lower nephron nephrosis. Fat emboli and petechia were also noted in the gastric mucosa and myocardium.

Case #2: FAT EMBOLISM FOLLOWING SOFT TISSUE TRAUMA ([redacted])

The patient was an 87 year old [redacted] man who was admitted to [redacted] on [redacted]/65 with severe prostatism for which a transurethral resection was performed on [redacted]65. The surgical specimen was noted to include fat adjacent to the prostate. The patient appeared to be recovering well for approximately 24 hours after the surgery. However, at that time he apparently had a syncopal episode, and fell from a chair in which he was sitting. On the following morning he suddenly became disoriented and later complained of pain in the chest, developed severe cyanosis and hypotension. He was treated with oxygen, Aramine, and 100 mg of heparin. He died 3 hours after the acute episode and 2 days following the surgery.

At autopsy there was acute pulmonary congestion and edema. The arterioles and small arteries of the lung were noted to contain numerous clear vacuole-like spaces; on Oil Red O stain these were shown to represent fat. Intravascular fat was likewise noted within the renal glomeruli. The cause of death was massive fat embolism.

Case #3: BILATERAL AVASCULAR NECROSIS OF BONE IN ALCOHOLIC MAN TREATED WITH STEROIDS [redacted]

The patient was a 63 year old [redacted] man who had been a longstanding alcoholic followed in this hospital primarily for severe exfoliated dermatitis for at least 15 years. The dermatitis was treated with large amounts of steroids, the dose of which the patient adjusted himself. In 1959, pain in the left hip was noted, and was subsequently diagnosed as avascular necrosis of the femural head. A fibular bone graft was inserted across the hip in 1960; however, the disease continued with progressive breakdown of both femural heads. In 1962 an arthroplasty was performed on the left hip and a prosthesis was inserted. The patient subsequently dislocated the hip and because of persistent pain and drainage the prosthesis was removed four months after its insertion. The patient had a prolonged convalescence, and three months after surgery he had a sudden episode of substernal pain accompanied by EKG findings of anterior myocardial infarction, and died 10 days later.

Postmortem examination showed only evidence of the myocardial infarction.

Case #4: FAT-INDUCED HYPERLIPEMIA CAUSING ABDOMINAL PAIN AND PAPILLEDEMA SIMULATING A BRAIN TUMOR [redacted]

The patient is a 36 year old [redacted] woman who was first seen in [redacted] in [redacted], 1955, complaining of severe diffuse lower abdominal pain. No diagnosis was established, and the patient was discharged after 5 days of hospitalization. She was apparently well until [redacted] of 1962, when she was seen in the allocations clinic because of diffuse episodic upper abdominal pain with nausea and vomiting relating to the ingestion of fatty meals. These symptoms persisted and became progressively worse over the next 9 months. In [redacted], 1962, severe headaches developed accompanied by nuchal rigidity, projectile vomiting, dizziness and lethargy. The patient was admitted on [redacted]/62 with a tentative diagnosis of brain tumor. On admission she had a temperature of 99.4°. Funduscopic examination revealed bilateral papilledema and one flame-shaped hemorrhage was noted on the right fundus; lipemia retinalis was present. Eruptive xanthoma were noted on the left elbow and the liver was found to be enlarged two finger breadths below the costal margin.

The patient's serum was grossly lipemic, a finding which was confirmed by a blood triglyceride level of 9,722 mg%. Cholesterol was 1,269 mg%. On electrophoresis the triglycerides migrated exclusively as chylomicra, confirming the diagnosis of fat-induced hyperlipemia. The patient was treated with intravenous glucose and hence a zero-fat diet. Clearing of the lipemia became obvious within 24 hours of removing dietary fat, triglyceride decreasing to 488 mg%, and cholesterol to 716 mg%. Simultaneously the patient's headaches and mental state improved. However, papilledema persisted and a pneumoencephalogram was carried out on [redacted]/63 with no abnormalities being found. The patient was discharged on a 20-30 gram fat diet and over the next three months the papilledema gradually subsided. She has been maintained on a low fat diet and followed in Metabolism Clinic over the past 5 years. During this time she has remained completely asymptomatic. Neither abdominal pains nor central nervous system symptoms have recurred. Both her triglyceride and cholesterol levels have remained within normal limits.

The patient was last examined on [redacted]/67, at which time her cholesterol was 242, triglyceride 151.

Case #5: CHOLESTEROL EMBOLI characterized by pain in the lower extremities, renal failure, hepatosplenomegaly, abdominal pain and petechiae [redacted]

The patient is a 61 year old [redacted] man who had been a known alcoholic for many years. He was first admitted to the medicine service in [redacted], 1960, with a history of progressive weakness, 20 lb. weight loss, and shortness of breath of approximately one year's duration. He had had frequent epistaxis for 6 months. Edema of the lower extremities had been present for five months and had progressed to the point of anasarca on admission. Over the month prior to admission the patient had begun to experience severe shooting pains in the legs and thighs and in addition had had bouts of severe abdominal pain. He had also noted the appearance of red spots on his trunk and lower legs for one month prior to admission.

Physical examination revealed a normal funduscopic examination; the lung fields were clear except for occasional rhonchi. The heart was slightly enlarged 1 cm beyond the midclavicular line, and a grade 2 systolic murmur was heard at the apex radiating slightly to the axilla. The abdomen showed the liver to be enlarged 6 cm below the costal margin; the spleen was likewise massively enlarged to the iliac crest. It is noteworthy that in retrospect a left upper quadrant mass was present on an outpatient visit in [redacted], 1960. Petechiae were noted over the chest, abdomen, and especially over the lower extremities.

The hemoglobin on admission was 8.6, white count 2,680, platelet count 90,000. Urinalysis showed a trace to 1+ albumin, with microscopic hematuria. Serology was negative. Stool guaiac was persistently 3+; BUN 92 mg%; creatnine 3.4; uric acid 9.0. The total serum protein was 8.3 with an albumin of 2.0; globulin 6.8; sodium 128; cholesterol 135; bilirubin 1.5; ceph. floc. 3+/3+.

The elevated gamma globulin was found to be of the 7S variety on ultracentrifugal analysis; electrophoresis did not demonstrate a narrow based gamma globulin peak. Bone marrow demonstrated plasmacytosis. Liver biopsy showed only a nonspecific granulomatous reaction.

Hypertension with diastolic blood pressure of 110 mm was observed throughout the three month hospitalization. The patient was intermittently febrile with temperature varying from 99 to 101°. He had a gradual downhill course with a rising BUN to 150 mg%, increasing edema, and died on [redacted]61. Blood cultures on the day of death grew out aerobacter aerogenes.

While initially a diagnosis of Waldenstrom's macroglobulinemia was entertained, the most likely diagnosis was assumed to be multiple myeloma. The consensus, however, was that the patient's overall symptomatology could not be explained on the basis of cirrhosis, multiple myeloma, or lymphoma.

At autopsy the major findings were in the lung, kidney and spleen. The lung demonstrated numerous islands of granulation tissue with foreign body type giant cells surrounding typical cholesterol clefts. Small tubercle-like areas were noted in the spleen. Granulomatous reaction with giant cells and small cholesterol clefts were also observed in the mediastinal lymph nodes. Kidneys showed marked hyalinization of the glomeruli. The examination of the heart revealed a large 1 cm x 0.4 cm thrombotic plaque on the tricuspid value which on section showed the presence of endocarditis with marked thickening and calcification.

The presence of widespread cholesterol emboli was identified by polarizing light and finally by gas liquid chromatography. It was concluded that the patient had bacterial endocarditis with multiple cholesterol emboli involving the kidney, spleen, skin, and lungs.

Case #6: CHOLESTEROL EMBOLI characterized by severe pain in the lower extremities and eosinophilia [redacted]

The patient is a 78 year old [redacted] man who was admitted to the [redacted] Service on [redacted]/67 because of severe pain in the feet and lower legs for the previous four years. The pain had caused moderate discomfort until two years prior to admission when it gradually became much more persistent and severe to the point where the patient could not drive his car because the pressure of the foot pedal was too painful. The pain was no more severe at night than during the day and was unrelated to activity. The past history is significant in that the patient had a probable myocardial infarction approximately five years ago.

Physical examination was completely normal except for atrial fibrillation. The patient's hemoblobin was 17.1, white count 9,900 with 10% eosinophilia. BUN was 25; total protein 7.3; albumin 4.4; globulin 2.9. The patient had a slightly abnormal glucose tolerance test and muscle capillary basement membrane width was 1784A, clearly in the diabetic range. For this reason the possibility of diabetic neuropathy was seriously entertained. The sections of the smaller arteries of the muscle biopsy, however, revealed definite cholesterol emboli. The patient has been treated unsuccessfully with Dilantin.

Case #7: TRANSPLANT PNEUMONIA possibly involving fat embolization [redacted]

The patient is a 48 year old [redacted] woman who was well until [redacted] 1967 when she developed uremia and hypertension leading to coma and convulsions. On [redacted] 1967 she was admitted to [redacted] for a renal transplant, and after being matched with her son, she was begun on Imuran and 100 mg Prednisolone. The transplant was preformed on [redacted] High doses, i.e. 80-100 mg. of Prednisolone were continued and the patient was given post-operative irradiation to the transplant area. Except for a draining abscess at the wound site the patient did well until October 20, i.e. two months after surgery. At that time she developed a cough with left pleuritic chest pain. Urine output decreased to 300 cc. and the patient became lethargic and irritable. On admission rales were heard throughout the left chest and ecchymotic spots were seen on her face, arms and legs. The BUN was 81, creatinine 2.8 mgs%, hemoglobulin 7.8. X-ray showed infiltration in both upper and lower lobes. Respiratory difficulty continued. A pO_2 was 200 on 100% oxygen. Eleven hours after admission the patient had a cardiac arrest and could not be resuscitated.

Table 1

LIPID EMBOLI

Types	Fat Emboli		Hyperlipemia	Cholesterol Emboli
Source of Fat Embolism	Bone Marrow	Fat or liver	Diet (exogenous) Liver(endogenous)	Atherosclerotic Plaques
Composition of Lipid Emboli	Particulate containing Fat & Marrow	Globule of Fat	Lipoproteins, i.e. Chylomicra or very low density particles	Cholesterol Crystals
Schematic			 Protein Coat	
Size Range	5 - 40 μ	5 - 20 μ	0.1 - 3.5 μ	50 - 500 μ
Causes of Embolization	Trauma Osteomye-litis	Fatty Liver induced with: 1. Steroids in large doses 2. Alcohol Adipose Tissue: 1. Trauma 2. Pancreatitis	1. Fat-induced (exogenous) hyperlipemia (severe) 2. Rarely carbo-hydrate (endogenous) hyperlipemia	Rupture of Atheromatous Plaques with release of Cholesterol

Table 2

TYPICAL FAT EMBOLISM SYNDROME

1. History of fracture, symptom-free interval 24-48 hours
2. Dyspnea, tachypnea, desaturation unrelieved by O_2
3. Fever
4. Petechiae - upper half of body
5. Anemia
6. Confusion, aggitation, coma and death

Table 3

INCIDENCE OF TRAUMATIC FAT EMBOLIZATION

	Incidence of Pulmonary Fat Embolism %
AUTOPSY (Ref. 49)	
Battlefield	86
Civilian	89
Routine Autopsies	
Medical	14
Surgical	36
CLINICAL (Ref. 31)	
Fracture	60
Soft Tissue	26
Mortality in Clinical Fat Embolism	10

Table 4

FAT EMBOLI AFTER CLOSED-CHEST MASSAGE (Ref. 18)

1. 35% of patients after cardiac massage have rib fractures.

2. All but one with rib fractures had pulmonary fat emboli.

3. But 2/3 of patients without fractures also had emboli after closed-chest massage.

4. All patients with significant (> 20/lpf) pulmonary emboli had cerebral emboli.

5. In control patients (50) without cardiac massage, pulmonary fat emboli was found in only one.

Table 5

DIAGNOSTIC TESTS FOR FAT EMBOLISM

1. Urine fat (Ref. 12, 31).

   a) Collect urine in bladder since fat floats.
   b) Collect in volumetric, i.e. narrow neck, flask.
   c) Remove upper layer, stain with Oil Red O or Sudan III.

2. Sputum fat (Ref. 1, 31, 32) very non-specific

3. Renal biopsy - fat stain (Ref. 1) (Probably single test).

4. Biopsy of Petechial fat stain, but usually no fat seen.

5. Spinal fluid fat (Ref. 35)

6. Serum lipase (elevated only after 4th day and not specific)

Table 6

LETHAL DOSE OF RABBIT FAT IN RABBIT (Ref. 46)

(There is approximately 2 ml of fat in one rabbit femur)

Injected Dose (ml)	Treatment	Mortality %
0.3	-	0
0.9	-	17
1.1	-	50
1.1	80% O_2	0

Table 7

INCIDENCE OF FAT EMBOLI IN FATTY LIVER vs. TRAUMA (Ref. 66)

	Incidence of Pulmonary Emboli	Density of Emboli *(per lpf)*	
Bone Trauma	91%		37 (1 - 192)
		Fatal	(23 - 192)
Soft Tissue	100%		34 (1 - 154)
		Fatal	(10 - 154)
Fatty Liver	78%		7 (0.5 - 34)
		Fatal	(4.0 - 72)
Control	≦ 11%		3

Table 8

SYNDROME OF CHOLESTEROL EMBOLIZATION

1. Severe, often sudden, pain in feet and legs with purple mottling of feet - livedo reticularis; gangrene
2. Abdominal pains acute simulating pancreatitis
3. Hypertension, renal
4. Albuminuria
5. Renal failure
6. Eosinophilia
7. Men > women

Table 9

DISTRIBUTION OF CHOLESTEROL EMBOLI

IN 92 PATIENTS WITH CHOLESTEROL EMBOLISM

Organ	Percent of Patients with Organ Embolized
Kidney	81
Pancreas	56
Spleen	47
Adrenal	19
Brain	13
Thyroid	12

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5. Robb-Smith, A.H.T. Pulmonary fat-embolism. Lancet, Feb. 1, 1941, p. 135.

At postmortem 81% of fatal accident cases have fat emboli to lung. Denies presence of fat emboli in non-traumatic deaths. Believes fat emboli a major cause of death in 25% of fatal accidents.

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Pulmonary fat emboli found in 90% of battle casualties. Fat embolism is of clinical significance in about 10-20%, but feels that pulmonary symptoms are minor.

7. Peltier, L.F. An appraisal of the problem of fat embolism. Intern. Abstracts of Surgery 104:313, 1957.

A general review of author's view of fat embolization. Believes fat embolism is a major cause of death following fractures.

8. Warren, S. Fat embolism. Amer. J. Path. 22:69, 1946.

Examined 100 cases of fat embolism. Pulmonary edema was especially prominent with 31% having cerebral emboli often with only minimal pulmonary emboli. Femur and/or tibial fractures accounted for 82% of cases.

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Again de-emphasizes significance of pulmonary emboli, believing that cerebral emboli are the major cause of symptoms and death.

10. Evarts, C. M. Diagnosis and treatment of fat embolism. JAMA 194:899, 1965.

A very brief review of fat embolism syndrome with report of one case. Advocates use of heparin and Dextran 40, 500 ml q 12 h.

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DISEASE OF BONE can also cause release of marrow-fat emboli:

Osteomyelitis

21. Broder, G. Systemic fat embolism following acute primary osteomyelitis. JAMA 199:150, 1967.

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22. Shelley, W. M. and Curtis, E. M. Bone marrow and fat embolism in sickle cell anemia and sickle cell-hemoglobin C disease. Bulle. Johns Hopkins Hosp. 103:8, 1958.

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TREATMENT of traumatic fat emboli

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100% Oxygen

40. Oxygen 100% IPPB. See ref. 15 and 16.

PATHOGENESIS OF TRAUMATIC FAT EMBOLISM

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Incidence of fat emboli in fracture and soft tissue injury noted. In rats 0.05 ml of oil is not normally fatal but after ischemia to a leg same dose kills 70% of rats. Conclude that traumatic release of fat explains fat embolism shock.

50. Swank, R. L. and Dugger, G. S. Fat embolism. A clinical and experimental study of mechanisms involved. Surg., Gyne. & Obstet. 98:641, 1954.

Severe contusions of muscle did not cause free fat globules to appear in normal rabbit blood. Fat rabbits have more emboli after a fracture than thin rabbits, i.e. more fat to mobilize (but also more chylomicra).

51. Glas, W. W. et al. An experimental study of the etiology of fat embolism. Amer. J. Surg. 91:471, 1956.

To resolve "mechanical" vs. "humeral" theories:

1. Determine if fat in marrow of one rabbit femur is sufficient to kill a second rabbit. It is.
2. Determine if breaking a bone leads to immediate embolization Same in a few minutes as at 24 hours.
3. Injected stained fat into marrow, then broke the bone, and found fat in lung was stained. All experiments favor simple mechanical theory.

52. Fuchsig, P., et al. A new clinical and experimental concept on fat embolism. The New Eng. J. Med. 21:1192, 1956.

Emphasizes the extent of the hemorrhage average 1400 ml femoral fracture at the site of most fractures and believes that shock increases fat absorption. States with no real data that fat reaches lung via thoracic duct.

53. Jones, J. P. and Sakovich, L. Fat embolism of Bone. J. Bone and Joint Surgery 48-A: 149, 1966.

Injected lipiodol into femoral artery will produce emboli to bone and especially large emboli to femoral head. By x-ray it takes 12-18 hours to "impact" in bone and accumulates in lung for two weeks.

54. Szabo, G., Serenyi, P., and Kocsar, L. Fat embolism: fat absorption from the site of injury. Surgery 54:756, 1963.

Free fat injected into muscle is absorbed slowly into the blood probably over many days. Lymphatic absorption is negligible.

How can large fat globules get through the lung?

55. Tobin, C. E. Arteriovenous shunts in the peripheral pulmonary circulation in the human lung. Thorax 21:197, 1966.

Glass spheres 200 μ in diameter injected into human pulmonary artery at postmortem will pass directly into pulmonary veins via a-v shunts which are capable of marked dilatation.

56. Swank, R. L. and Hain, R. F. The effect of different sized emboli on the vascular system and parenchyma of the brain. J. Neuropath. & Exp. Neur. 11:280-299, 1950.

Injected paraffin emboli into dog carotid artery. Both large 35 and 60 μ and small 4 to 17 μ emboli will pass through the cerebral capillaries which are 5-8 μ in diameter but both sizes produce infarcts.

57. Lowenfels, A. B. and Barbieri, R. Survival after repeat pulmonary fat embolus. Arch. Surg. 93:517, 1966.

Prior sublethal fat embolization with oil increases survival of second oil injection 3-4 weeks later. But 5 of 42 dogs developed paraplegia suggesting bypassing (shunting) of fat on second injection.

58. Peltier, L. F. Surgery 40:657 and 665, 1956.

Suggests that lipase released free fatty acids from pulmonary fat emboli to cause pulmonary symptoms. Actually no evidence is presented to support this concept.

CONCLUSIONS:

1. *Traumatic fat embolization is best explained as being due to direct release of fat from bone marrow and/or soft tissue fat. There is no real evidence to support the "physico-chemical theory" of traumatic fat embolization.*

2. *Release of free fatty acids from fat emboli has not yet been demonstrated to play a role in tissue injury of fat embolism syndrome.*

III. FAT EMBOLI FROM HEPATIC FAT

EXPERIMENTAL

59. Hartroft, W. S. Fat emboli in glomerular capillaries of choline-deficient rats and of patients with diabetic glomerulosclerosis. Amer. J. Path. 31:381, 1955.

Renal fat emboli - presumably from liver - regularly present in rats with fatty liver induced with choline deficiency.

60. Hartroft, W. S.and Ridout, J. H. Pathogenesis of the cirrhosis produced by choline deficiency. Amer. J. Path. 27:951, 1951.

Demonstrates fat in fatty liver of rats and man in fatty cysts moving into hepatic vessels.

Well-documented massive fat emboli in CCl_4 poisoning

61. MacMahon, H. E. and Weis, S. Carbon tetrachloride poisoning with macroscopic fat in the pulmonary artery. Amer. J. Path. 5:623, 1929.

CCl_4 ingestion in an alcoholic resulted in release of large amounts of hepatic fat into pulmonary accumulation and lesser renal and brain fat emboli.

Alcoholic fatty liver in man can release fat emboli

62. Lynch, M.J.G., Raphael, S. S., Dixon, T. P. Fat embolism in chronic alcoholism. The Lancet, July 20, 1957, p. 123.

First report of incidence of pulmonary fat emboli in alcoholic fatty liver (71%) and in alcoholic cirrhosis (67%). Embolization is "heavy" in 25%.

63. Lynch, M. J. G., Raphael, S. S., and Dixon, T. P. Fat embolism in chronic alcoholism. Arch. Path. 67:68, 1959.

Small numbers of pulmonary fat emboli are seen in 78% of cases of alcoholic fatty liver. In five selected cases pulmonary and cerebral fat emboli may have been major cause of death.

64. Durlacher, S. H., Meier, J. R., Fisher, R. S., and Lovitt, W. V. Sudden death due to pulmonary fat embolism in persons with alcoholic fatty liver. Amer. J. Path. 30:633, 1954.

In 25 cases of alcoholic fatty liver at autopsy, 5 showed "massive pulmonary fat embolism".

65. Fadell, E. J. and Sullivan, B. H. Fatty liver and fat embolism. U. S. Armed Forces Med. J. 8:114, 1957.

In case of fatal alcohol intoxication autopsy showed severe fatty liver and many fat emboli in kidney, lung and brain.

66. Lynch, M. J.G. Brain lesions in chronic alcoholism. Arch. Path. 69:116, 1960.

Fat embolism appeared to be chief cause of death in 4 of 11 alcoholics. Believes fat emboli may provide explanation for D.T.S.

67. Cammermeyer, J. and Gjessing, R. Fatal myocardial fat-embolism in periodic catatonia with fatty liver. Acta Medica Scandinavica 139:358, 1951.

Report myocardial infarction from fat embolism thought to be derived from fatty liver.

STEROIDS will cause fatty liver and widespread fat emboli in rabbits.

68. Moran, T. J. Cortisone-induced alterations in lipid metabolism. Arch. Path. 73:300, 1962.

After 21 days on high doses of steroids almost all (43/44) rabbits show fatty liver and pulmonary fat emboli.

STEROIDS can cause FAT EMBOLISM

69. Hill, R. B. Fatal fat embolism from steroid-induced fatty liver. The New Eng. J. Med. 265:318, 1961.

First case report of documented fat embolism originating from fatty liver induced with 11 weeks of 100 mg prednisone for rheumatic fever. Fat found in vessels of liver, lung, brain, pancreas and kidneys.

70. Jones, J. P., Engleman, E. P., and Najarian, J. S. Systemic fat embolism after renal homotransplantation and treatment with corticosteroids. N. Eng. J. Med. 273:1453, 1965.

Describe 4 cases of fat embolization during withdrawal from large doses of steroids following renal transplants. In 2 resulting deaths, fatty liver and widespread fat emboli documented. Suggest that transplant pneumonia and some "rejection crisis" may be due to fat embolism.

71. Jones, J.P., and Engleman, E. P. Fat embolization complicating hypercortisonism. Arth. & Rheum. 8:448, 1965.

Two further cases of steroid therapy followed by suggestive evidence of fat embolization syndrome.

AVASCULAR NECROSIS OF BONE

72. Kahlstrom, S. C., Burton, C. C., and Phemister, D. B. Aseptic necrosis of bone. Surg. Gyne. & Obstet. 68:631, 1939.

First suggest fat embolism as cause of avascular necrosis of bone.

73. Hastings, D. E., and Macnab, Ian. Spontaneous avascular necrosis of the femoral head. Canadian J. Surg. 8:68, 1965.

A good review of avascular necrosis of femoral head with emphasis on steroid etiology. Six of ten patients with typical disease had been on high doses of steroids for 18 or more months.

74. Mankin, J. H. and Brower, T. D. Bilateral idiopathic aseptic necrosis of the femur in adults: "Chandler's Disease". J. Hosp. for Joint Diseases. 23:42, 1962.

Sixty percent of patients (3/5) with Chandler's disease are alcoholic. Three had hepatomegally but authors think fat embolism unlikely.

75. Patterson, R. J., Bickel, W. H., and Dahlin, D. C. Idiopathic avascular necrosis of the head of the femur. J. Bone and Joint Surg. 46-A:267, 1964.

In Mayo Clinic experience avascular necrosis of femur head is associated with alcoholism, 17%,and steroid therapy,10%.

76. Madell, S. H. and Freeman, L. M. Avascular necrosis of bone in Cushing's Syndrome. Radiology 83:1068, 1964.

Avascular necrosis of bone can be caused by adrenal adenoma.

77. Jones, J. P., and Engleman, E. P. Osseous avascular necrosis associated with systemic abnormalities. Arth. & Rheum. 9:728, 1966.

Review of avascular necrosis not due to trauma. Suggest fat embolism as a cause of avascular necrosis.

78. Jones, J. P., et al. Fat embolization as a possible mechanism producing avascular necrosis. Arth. & Rheum. 8:449, 1965.

Find multiple fat globules in arterioles of necrotic femoral heads of one alcoholic and one iatrogenic Cushings. Only really direct evidence that fatty emboli may cause femoral head necrosis.

IV. CHYLOMICRON - EMBOLIZATION

Chylomicra are usually smaller than red cells

79. Kay, D., and Robinson, D. S. The structure of chylomicra obtained from the thoracic duct of the rat. Quar. J. Exper. Physiol. 47:258, 1962.

Chylomicra from thoracic duct range from 100 to 3500 mμ (3.5μ).

But particles of fat less than 7 μ can stop blood flow

80. Branemark, P.I., and Lindstrom, J. Microcirculatory effects of emulsified fat infusions. Circu. Res. 15:124, 1964.

Injection of 5 μ diameter fat emulsion 3 gm/kg into rabbit will decrease average capillary of blood flow by 1/5th, and will block flow in some capillaries completely.

Moreover, in experimental animal chylomicra, i.e. a single high fat meal can kill.

81. Swank, R. L., Glinsman, W., and Sloop, P. The production of fat embolism in rabbits by feeding high fat meals. Surg. Gyne. & Obstet. 110:9, 1960.

43% of rabbits fed 6.5 gm/kg in a single feeding die of fat embolism to lung, kidney and brain.

In man, chylomicra can cause angina

82. Kuo, P. T. and Joyner, C. R. Angina pectoris induced by fat ingesion in patients with coronary artery disease. JAMA, July 23, 1955, p. 1008.

Fourteen original attacks reported in six patients by a single fat meal. EKG changes and angina seen 3-5 hours after meal.

Reversible with heparin

83. Kuo, P. T. and Joyner, C. R. Effect of heparin on lipemia-induced angina pectoris. JAMA 163:727, 1957.

Heparin - 5 to 25 mg IV caused prompt (10 min) relief of angina of alimentary lipemia.

Fat and carbohydrate-induced hyperlipemia

84. Ahrens, E. H., et al. Carbohydrate induced and fat induced lipemia. Trans. Asso. Amer. Phys. 74:134, 1961.

Differentiates fat and carbohydrate induced lipemias. Pancreatitis characteristic of fat induced, rare in carbohydrate induced.

Hyperlipemia causes pancreatitis and neurologic symptoms

85. Poulsen, H. M. Familial lipaemia. Acta Med. Scand. 138:414, 1950.

Suggests hyperlipemia is responsible for pancreatitis. Patient had abdominal pain, headache, aggitation, delirium with hyperlipemia attack.

86. Corazza, L. J. and Myerson, R. M. Essential hyperlipemia. Amer. J. Med. 22:258, 1957.

Neurologic signs and seizures noted in patient with hyperlipemia. Signs and symptoms promptly subsided on low fat diet.

Hyperlipemia causes pancreatitis; pancreatitis does not cause hyperlipemia.

87. Klatskin, G., and Gordon, M. Relationship between relapsing pancreatitis and essential hyperlipemia. Amer. J. Med. 12:3, 1952.

Presents the case for hyperlipemia producing pancreatitis probably by fat embolization. Argues that there is no evidence that pancreatitis causes hyperlipemia.

88. Greenberger, N. J., et al. Pancreatitis and hyperlipemia. Medicine 45: 161, 1966.

1. Hyperlipemia is observed in only 3/25 patients with pancreatitis.
2. In each of these three, hyperlipemia preceded pancreatitis.

V. CHOLESTEROL EMBOLIZATION - CLINICAL SYNDROMES

89. Retan, J. W. and Miller, R. E. Microembolic complications of atherosclerosis. Arch. Int. Med. 118:534, 1966.

Excellent, complete review of clinical syndromes produced by atheromatous emboli.

90. Moldveen-Geronimus, M., and Merriam, J. C. Cholesterol embolization from pathological curiosity to clinical entity. Circulation 35:946, 1967.

Brief review with two cases emphasizing relationship between anticoagulant therapy and cholesterol embolization.

91. Feder, W., and Auerbach, R. "Purple Toes": an uncommon sequela of oral coumarin drug therapy. Ann. Int. Med. 55:911, 1961.

In six patients painful purple mottling of feet occurred 3 to 8 weeks after anticoagulation therapy.

92. Richards, A. M., et al. Cholesterol embolism. A multiple-system disease masquerading as polyarteritis nodosa. Amer. J. Cardio. 15:696, 1965.

Excellent review of the syndrome of cholesterol embolization stressing the resulting arteritis leading to abdominal and leg pain, hypertension and renal failure. Increased globulin and eosinophilia noted and not easily explained.

93. Fisher, E. R., Hellstrom, H. R. and Myers, J. D. Disseminated atheromatous emboli. Amer. J. Med. 29:176, 1960.

First to emphasize the similarity of cholesterol embolic syndrome to polyarteritis nodosa.

94. Handler, F. P. Clinical and pathologic significance of atheromatous embolization, with emphasis on an etiology of renal hypertension. Amer. J. Med. 20:366, 1956.

Reports 13 cases of cholesterol embolization with widespread arteritis. Suggests that hypertension is due to renal emboli.

95. Probstein, J. G., Joshi, R. A., and Blumenthal, H. T. Atheromatous embolization. AMA Arch. Surg. 75:566, 1957.

Review of autopsy findings of their 23 cases of cholesterol embolization. Kidney and pancreas are most common sites of embolization. Pancreatitis was found in 10 of the 12 patients with pancreatic emboli.

96. Hoye, S. J., et al. Atheromatous embolization. New Eng. J. Med. 261:128, 1959.

A case of gangrene of one foot with good pulses due to cholesterol emboli found also in kidney and brain.

97. Anderson, W. R., Richards, A. M., and Weiss, Leo. Hemorrhage and necrosis of the stomach and bowel due to atheroembolism. Amer. J. Clin. Path. 48: 30, 1967.

Describes a case of weight loss and recurrent GI hemorrhage in a 65 year old man accompanied by renal failure and hypertension. Muscle biopsy showed cholesterol emboli; at autopsy numerous cholesterol emboli of intestinal arteries.

Experimental production of cholesterol emboli

98. Flory, C. M. Arterial occlusions produced by emboli from eroded aortic atheromatous plaques. Amer. J. Path. 21:549, 1945.

Injected suspension of aortic plaques IV into rabbit in 7 days showed lesions identical to human cholesterol emboli with granular and giant cells.

99. Snyder, H. E. and Shapiro, J. A. A correlative study of atheromatous embolism in human beings and experimental animals. Surgery 49:195, 1961.

Injected cholesterol suspensions cause arteritis in one day, and giant cell granulomas in six days; lesions persist unchanged for at least five months.

100. Anderson, W. R., Richards, A. M., and Weiss, Leo. Hemorrhage and necrosis of the stomach and bowel due to atheroembolism. Amer. J. Clin. Path. 48: 30, 1967.

Injected atheromatous suspension into rabbit aorta caused GI artery emboli and intestinal hemorrhage.