FAT EMBOLISM DUE TO CARDIOPULMONARY BYPASS

A Senior Honors Thesis

Presented to

The Faculty of the Department of Biophysical Sciences

College of Arts and Sciences

University of Houston

by

Kenneth P. Malloy

May 1974

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ABSTRACT

Cardiopulmonary bypass has been implicated as a cause of fat embolism resulting in pulmonary and cerebral complications. To determine whether cardiopulmonary bypass produces fat particles in the pulmonary circulation, 24 patients who underwent cardiopulmonary bypass for open-heart procedures were evaluated. Blood from the right atrium is sampled before, during and after cardiopulmonary bypass. The blood samples are centrifuged, stained, and examined microscopically. A statistically significant increase in the number and size of serum fat globules is noted during and immediately after medial division of the sternum. Of this group, 20 patients demonstrated fat embolization manifested by an increase in the number and size of the fat globules from one to three minutes following median sternotomy. These findings may account for some intraoperative as well as postoperative respiratory complications.

TABLE OF CONTENTS

TABLE OF FIGURES

INTRODUCTION

Modern Advances in Open Heart Surgery

Open heart surgery is a recent medical development in the surgical treatment of diseases of the heart and the great vessels. Notable pioneers who have paved the way of this frontier include Gibbon,[1-5] Lillehei,[6-8] and Cooley.[9,10] One of the greatest advances made in thoracic surgery is the ability to operate on the non-beating heart. Although many have contributed to the development of extra-corporeal circulation, the original concept of a machine to completely bypass the cardiopulmonary circuit belongs to Gibbon. The idea struck him while seeing a patient expire due to an inoperable (at that time) massive pulmonary embolus. Lillehei described the benefits of cross circulation while repairing a ventricular septal defect using a donor (usually the mother) to supply oxygenated blood to the patient during the open heart procedure. Cooley developed cavae occlusion clamps. When these clamps are secured on the cavae total bypass of the heart and lungs is achieved without undue trauma to the superior or inferior vena cavae. A more recent advance in the field of cardiopulmonary bypass is hypothermia to avoid ischemic contracture of the heart (stone heart)[11] as described by Reed.[12]

Any multitude of procedures can be utilized to repair, or replace, the viable heart muscle depending on the type and extent of the disease involved— congenital or acquired. Among the most common congenital defects are atrial septal defects, ventricular septal defects, tetralogy of Fallot, and transposition of the great vessels. Until recently surgical intervention for acquired cardiac, other than valvular, lesions was rare. The heart transplant era was short and unstable. Use of the artificial heart as a treatment for severely diseased hearts was employed for an even shorter time. Since 1969 over 3000 patients have undergone operation at the Texas Heart Institute in whom athlerosclerotic lesions within the coronary arteries were bypassed according to the method described by Favaloro[13] and popularized by Wukasch[14] and Cooley.[15] These lesions are bypassed with a segment of the saphenous vein while the patient is on total cardiopulmonary bypass.

Fat Embolization during Open Heart Procedures

Cardiopulmonary bypass has been implicated by several investigators as a cause in the production of fat embolism resulting in pulmonary and cerebral complications.[16-22] Before cardiopulmanary bypass is instituted the sternum is divided by an electric saw to expose the heart. Conceivably, fat could enter the bloodstream during division of the sternum before cardiopulmonary bypass.[23,24] This concept was suggested by discovery of massive pulmonary fat embolization at autopsy in a patient who had undergone cardiac surgery at the Texas Heart Instutite. The patient had not received external cardiac massage nor had he demonstrated any other obvious site of origin for fat emboli. In order to test the hypothesis that mechanical sternal division may result in the production of fat emboli, a protocol was designed to search for free fat in the right atrium before, during, and after median sternotomy.

EXPERIMENTAL METHODS

Surgical Protocol

The patients were randomly selected before undergoing cardiac procedures requiring median sternotomy and cardiopulmonary bypass. Serial 7 ml aliquots of blood were aspirated from a central venous pressure (CVP) catheter inserted into the right atrium via either subclavian vein of the patient. The catheter must be in the right atrium to gain sufficient mixing of the blood inferior to the azygos vein, responsible for the venous return of the right intercostal and mediastinal veins. In the first series, fourteen adult patients who underwent operation between July and October, 1973 were submitted to this surgical protocol:

Sample 1	Before incision (control)
Sample 2	After incision (subcutaneous fat division)
Sample 3	During sternal division
Sample 4	30 seconds after sternal division
Sample 5	1 minute after injection of heparin
Sample 6	15 minutes after institution of total cardiopulmonary bypass (drawn from arterial reservoir)
Sample 7	1 minute after injection of protamine to reverse heparin
Sample 8	4 to 5 hours postoperatively

In this series, two patients were eliminated from the study because of technical failure to obtain adequate samples of blood. In the second series, ten adult patients who underwent operation between January and March, 1974 were submitted to this surgical protocol:

Sample 1	Before incision (control)
Sample 2	During sternal division
Sample 3	1 minute after sternal division
Sample 4	2 minutes after sternal division
Sample 5	3 minutes after sternal division
Sample 6	4 minutes after sternal division
Sample 7	5 minutes after sternal division
Sample 8	10 minutes after sternal division

Laboratory Protocol

The method of analysis for free fat was modified from the procedure described by Huaman.[25] Each sample of blood is placed in an evacuated test tube with 10.5 mg ethylenediaminetetraacetic acid (EDTA) to inhibit thrombus formation. Samples are centrifuged* at 4000 rpm at 2275 g. Fat globules are driven to the top by centrifugation. The uppermost portion of the serum is pipetted to mark 1 of a white blood cell dilution pipette (Figure 1). Oil-Red-O** is added to mark 11. The pipettes are shaken mechanically for ten minutes. The contents are released into a hemacytometer counting chamber that is degreased with Freon.*** Gross fat particle counts are done at the original magnification of x40. Size measurements are performed at the original magnification of x450. Only those particles visible and clearly stained are counted. The number of globules per cubic millimeter of serum

*International Equipment Co.,Centrifuge PR-6
**J.T. Baker Laboratory Chemicals
***Dupont Corporation

was calculated:

$$\text{Fat globules/MM}^3 = \frac{N \times 10}{1.8}$$

where N is the number of globules counted, 10 the dilution factor,and 1.8 the volume of the hemacytometer counting chamber.

EXPERIMENTAL RESULTS

First Series

Of the twelve completed studies, ten were positive for fat globules (83%) and two were negative. A statistically significant increase in the number and size of serum fat globules is seen during division of the sternum and immediately thereafter (Figures 2 and 3). The total number and size of fat globules decreases during cardiopulmonary bypass. The postoperative samples show a further decrease in number, but an increase is noted in the size of these fat globules as compared to controls (Figures 4 through 8).

Second Series

All these patients demonstrate a peak "fat shower" between one and three minutes after sternal division. After three minutes following median sternotomy, the total number and size of the fat globules steadily decreases (Figures 9 and 10).

DISCUSSION

Fat embolization is the entrance of liquid fat into the circulation in the form of globules large enough to obstruct capillary beds. Clinical signs and symptoms are pulmonary congestion, delirium, edema, fever tachycardia, and the characteristic petechial rash.

Lower, in 1669, initiated scientific investigation in fat embolization by injecting milk into the vein of a rabbit's ear. In 1862 Zenker[26] was the first to recognize fat emboli in the pulmonary capillaries of man. Warthin[27] in 1913 reported fat embolization to be the most frequent cause of death in patients having fractures of the long bones. In 1941 Scuderi[28] described the roentgenographic appearance of fat embolization in the lungs.

Various causes have reportedly produced fat embolization including cardiopulmonary bypass,[16-22] external cardiac massage,[29-33] trauma to bones,[27,34-40] alcoholism,[34] poisonings,[34] high altitude flights,[34] and postpartum status.[25] Several theories attempting to explain the etiology of fat embolization have been proposed since 1924. In that year Gauss[38] described the entry of fat, liberated from bone marrow following fractures, into ruptured veins held open by rigid bone. Added support was given to this thesis by Peltier[37] in 1954. Cobb[41] in 1958 radioactively tagged emboli with I^{131}. The emboli were introduced into peripheral veins and carotid arteries in separate groups of dogs. Nearly all of the fat emboli were arrested by the lungs. When a large amount was infused the lungs ceased to serve as a natural filter. Fat embolization then took place in the cerebral region.

External cardiac massage without sternal fracture is a frequent precursor to fat embolization according to several investigators.[29-33] Jackson[33] believes that microfractures within the medulla of the ribs and sternum are responsible for this phenomenon.

Cardiopulmonary bypass has been implicated in the production of fat globulinemia,[21,42] and in elevation of blood lipid factors.[43] One possible explanation may be that direct blood-gas contact disrupts the surface tension or electrical charge of the lipo-protein elements of the blood, resulting in the coalescence of the lipid fractions into recognizable emboli.[16]

Various methods of preventing embolization have been proposed. Adams[16] reported that the addition of a non-ionic detergent (Pluronic F68) to the prime volume of cardiopulmonary bypass minimized this problem. Membrane oxygenators have been reported to decrease this phenomenon as compared to bubble oxygenators.[21,42] Caguin[17] demonstrated the reduction of fat globulinemia with the use of the intracardiac sump suction during cardiopulmonary bypass. Scudese[38] presented evidence of improvement in four of five patients with pulmonary fat emboli who were treated with 5% alcohol in 5% dextrose. He also recommended dextran and hypothermia to decrease the severity of emboli while also increasing the hemoglobin. Use of corticosteroids, as proposed by Wilson,[44] in such cases as fat embolism, is an interesting, yet controversial, method of treatment. He makes the claim that Solu-Medrol**** (methylprednisolone sodium succinate)

****Upjohn Company

stabilizes cell membranes, prevents tissue damage, and loss of organ function if adequate clinical doses are given before an irreversible state is reached. Cobb[41] observed that embolic fat becomes mobilized and metabolized approximately four days after the initial injury. The administration of heparin in smaller doses than required for anticoagulation produced more rapid mobilization and metabolism of fat emboli.[45]

CONCLUSION

To determine whether division of the sternum could produce fat emboli, 24 patients who underwent cardiac surgical procedures were studied. Serial samples of right atrial blood demonstrate a significant increase in the total number and size of fat globules during and immediately after sternal division; before cardiopulmonary bypass is instituted. Although multiple factors may be implicated, these findings demonstrate that sternal division alone produces significant fat embolization. This may account for some post-operative respiratory complications and indicates a need for development of methods for preventing this phenomenon. Validity of the use of heparin has been demonstrated in animals and patients with extensive fat embolization and presently appears to be the most promising approach in containing this problem.

FIGURE 1

White Blood Cell Dilution Pipette

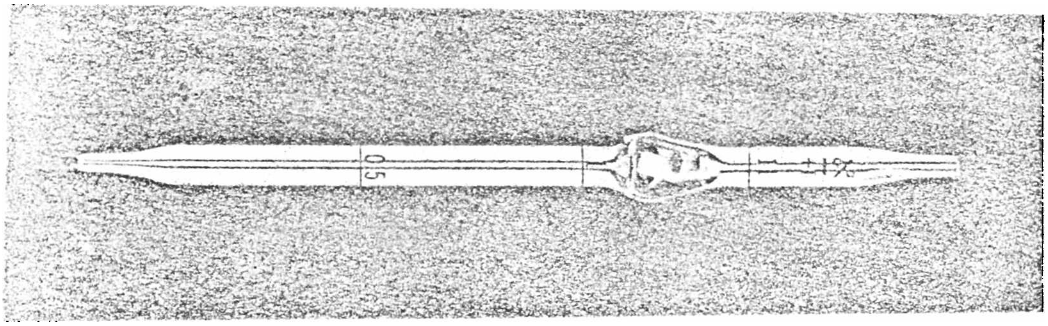
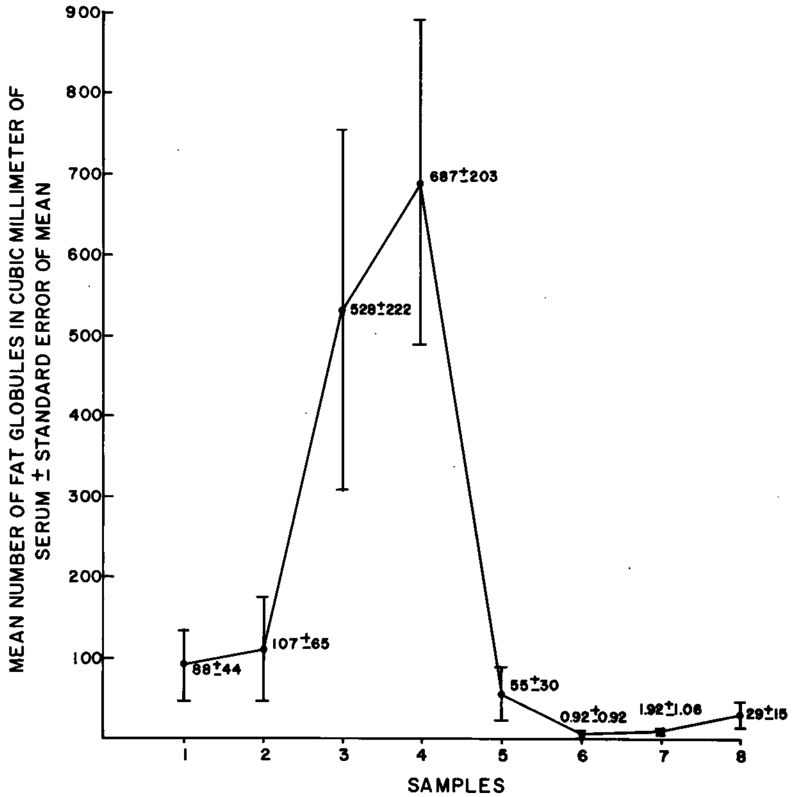


FIGURE 2

Number of Fat Particles per Serial Sample

Series One



MEAN NUMBER OF FAT GLOBULES IN CUBIC MILLIMETER OF SERUM ± STANDARD ERROR OF MEAN
900
800
700
600
500
400
300
200
100
687±203
528±222
107±65
88±44
55±30
0.92±0.92
1.92±1.06
29±15
1
2
3
4
5
6
7
8
SAMPLES

FIGURE 3

Maximum Globule Size Visualized in Counter per Serial Sample

Series One

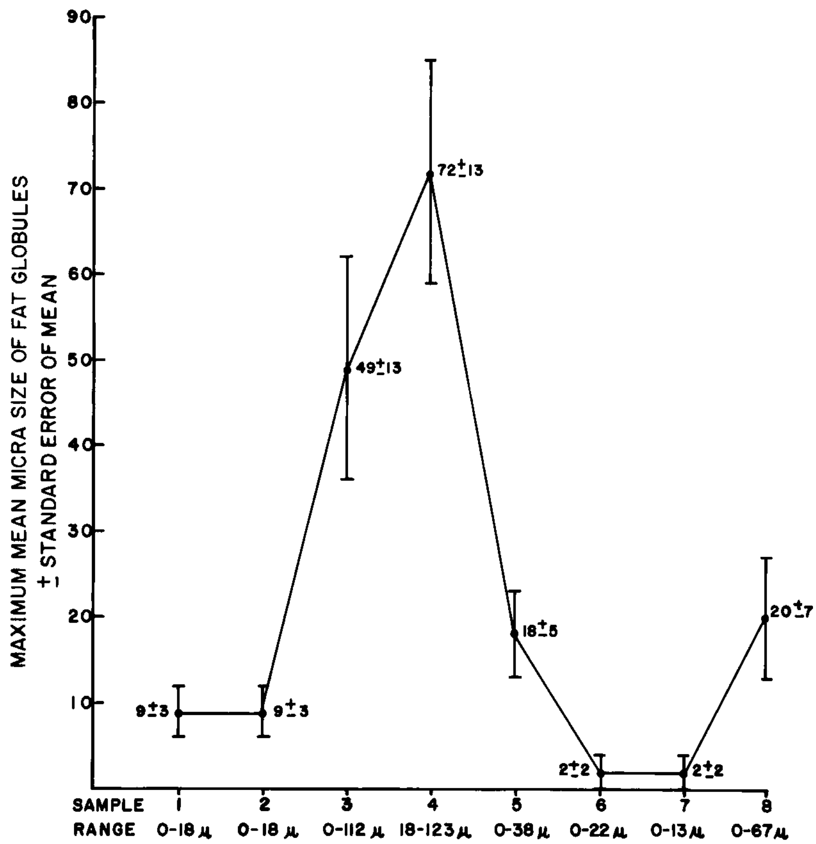

MAXIMUM MEAN MICRA SIZE OF FAT GLOBULES
± STANDARD ERROR OF MEAN
90
80
70
60
50
40
30
20
10
9±3
9±3
49±13
72±13
18±5
2±2
2±2
20±7
SAMPLE 1 2 3 4 5 6 7 8
RANGE 0-18 μ 0-18 μ 0-112 μ 18-123 μ 0-38 μ 0-22 μ 0-13 μ 0-67 μ

FIGURE 4

Photomicrograph of Sample 1 (control) in Hemacytometer

Original Magnification of x40

Note the Few Particles and Small Sizes

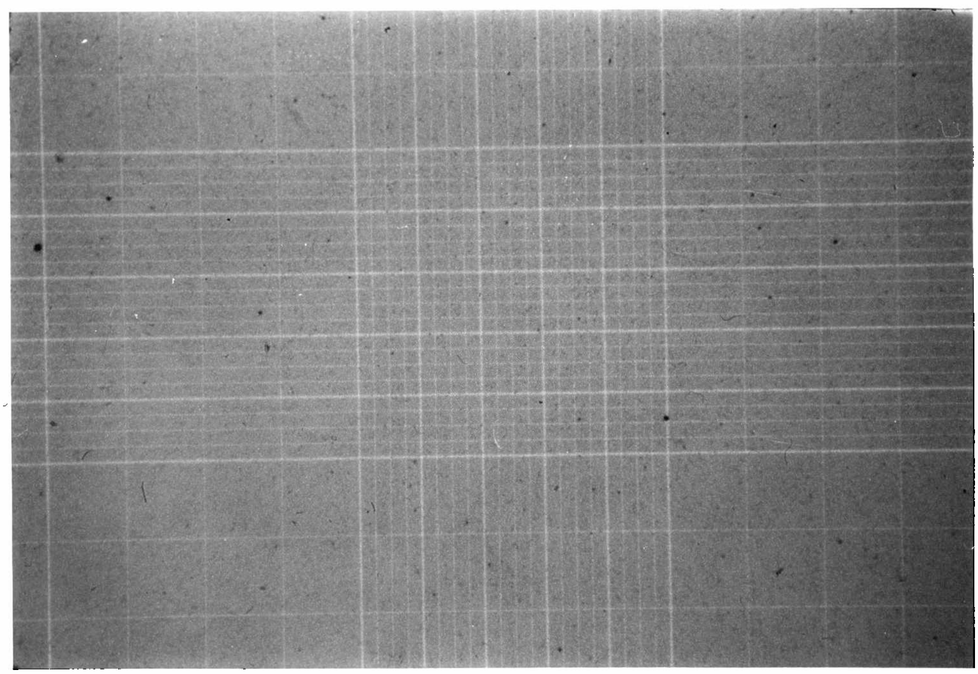


FIGURE 5

Photomicrograph of Sample 4 in Hemacytometer

30 Seconds after Sternotomy

Original Magnification of x40

Note the Increase in Size and Number Compared to Figure 4

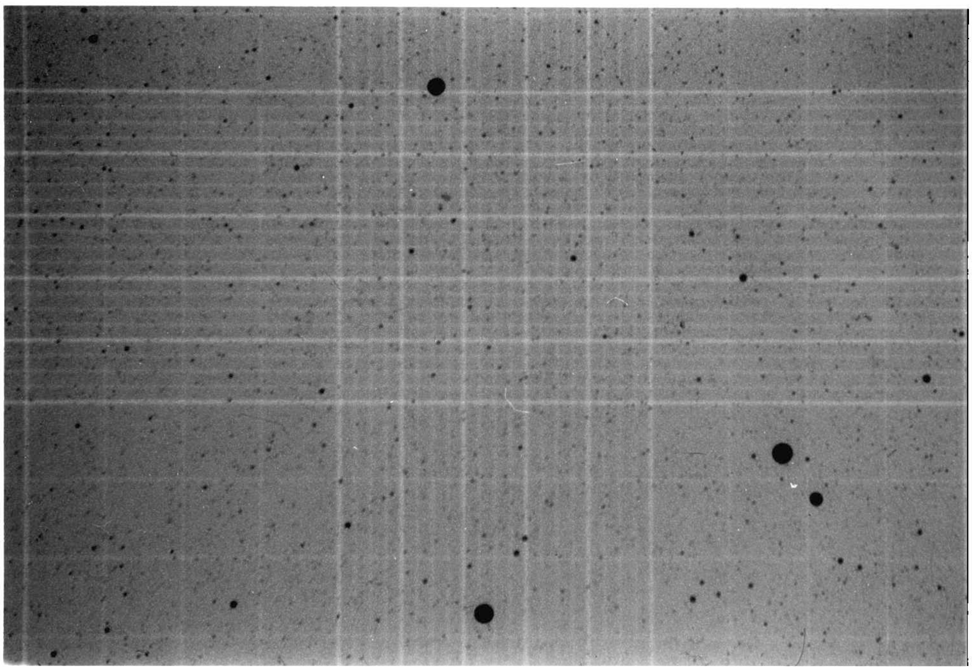


FIGURE 6

Photomicrograph of Fat Globules of Sample 4

30 Seconds after Sternotomy

Original Magnification of x450

Largest Globule 100μ in Diameter

Scale approximately 1 cm = 17μ

Note the Superimposition of Globules within the Suspension

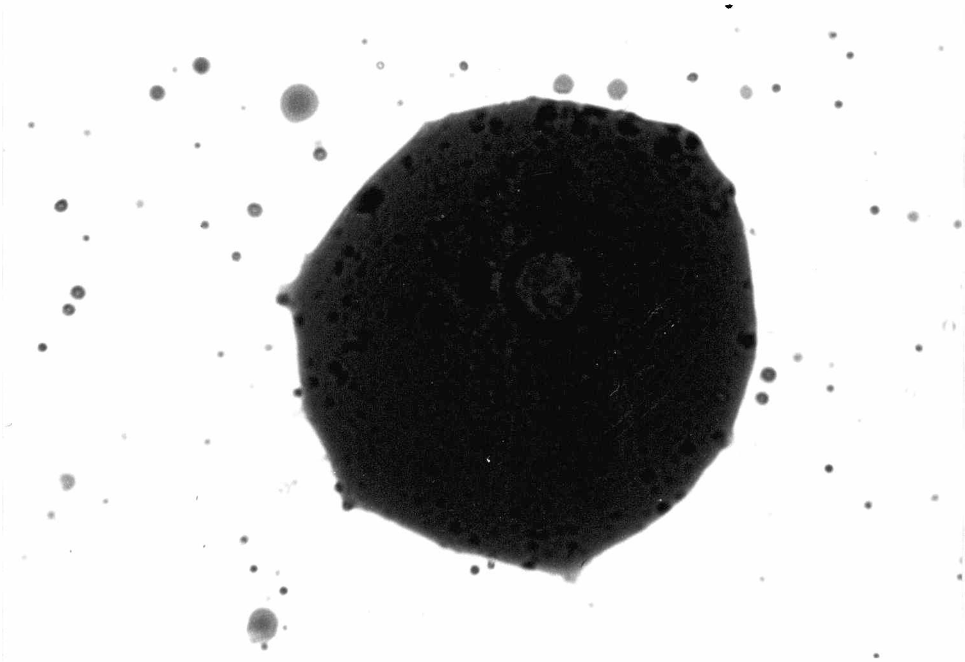


FIGURE 7

Photomicrograph of Fat Globules of Sample 4

30 Seconds after Sternotomy

Original Magnification of x450

Largest Globule 100μ in Diameter

Scale approximately 1 cm = 17μ

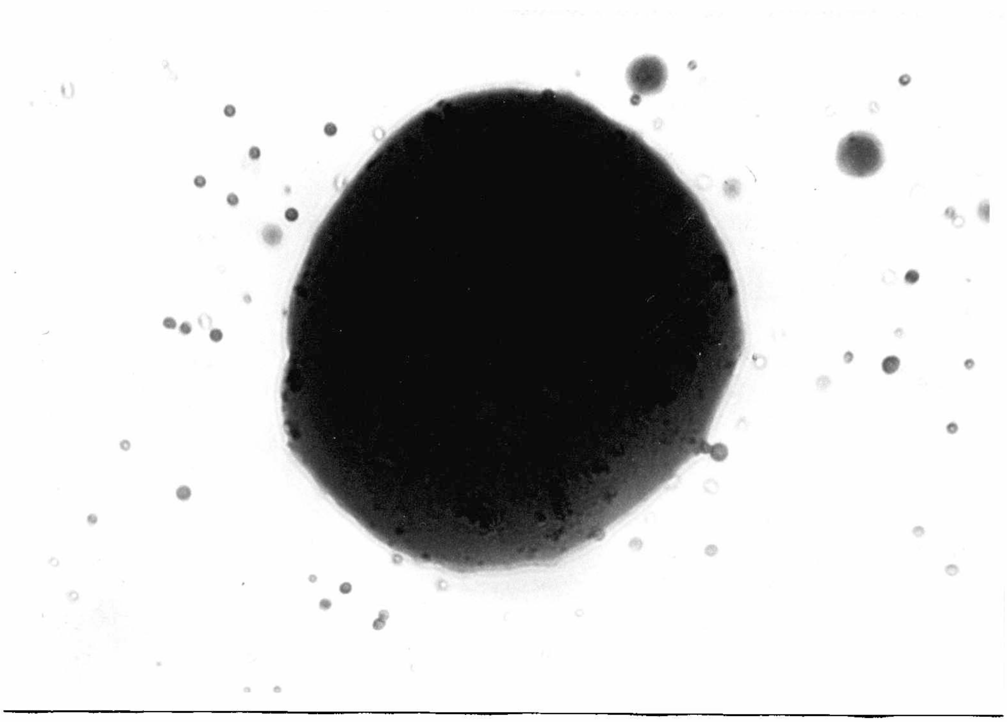


FIGURE 8

Photomicrograph of Sample 6 in Hemacytometer

15 Minutes on Total Bypass, taken from Arterial Reservoir

Original Magnification of x40

Note the Few Particles and Small Sizes

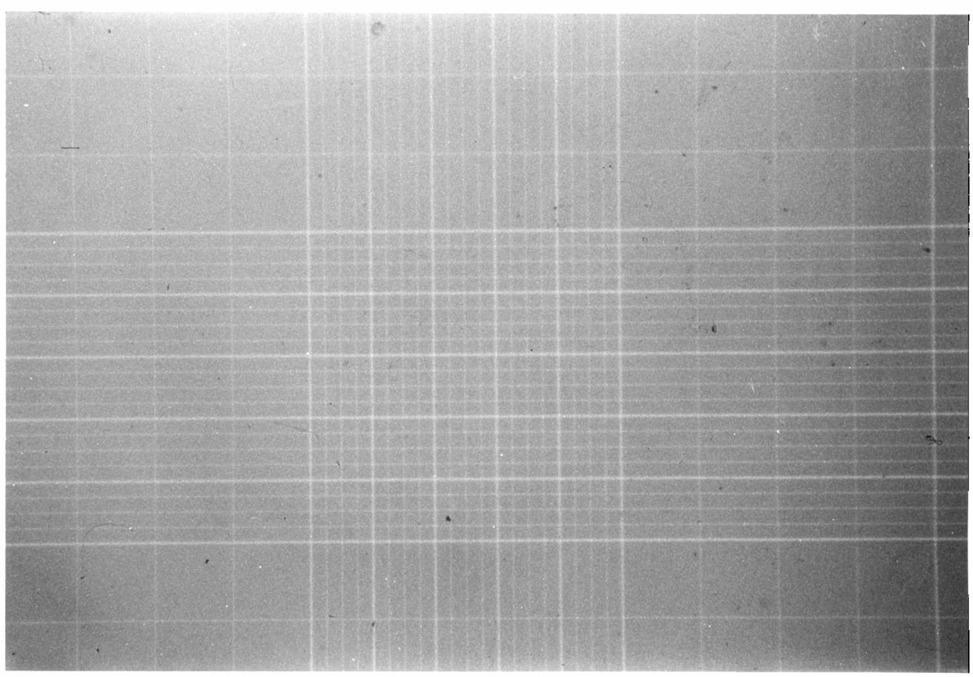


FIGURE 9

Number of Fat Particles per Serial Sample

Series Two

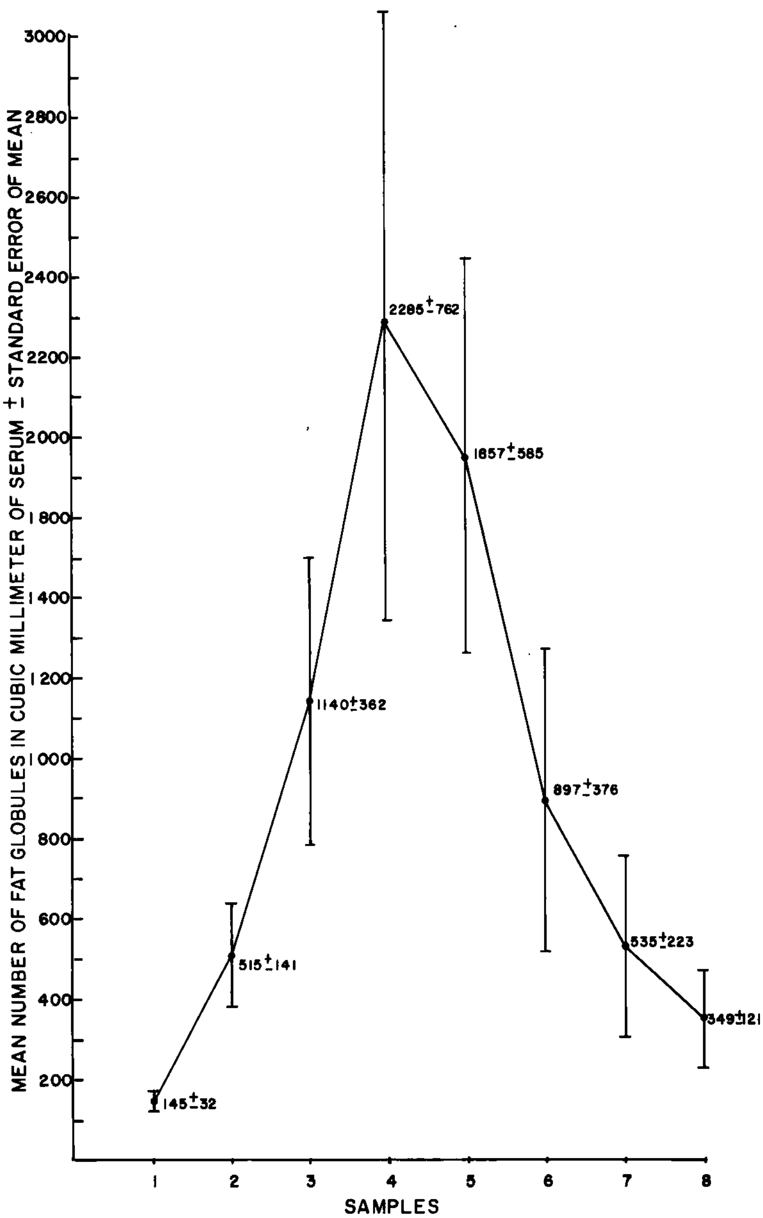
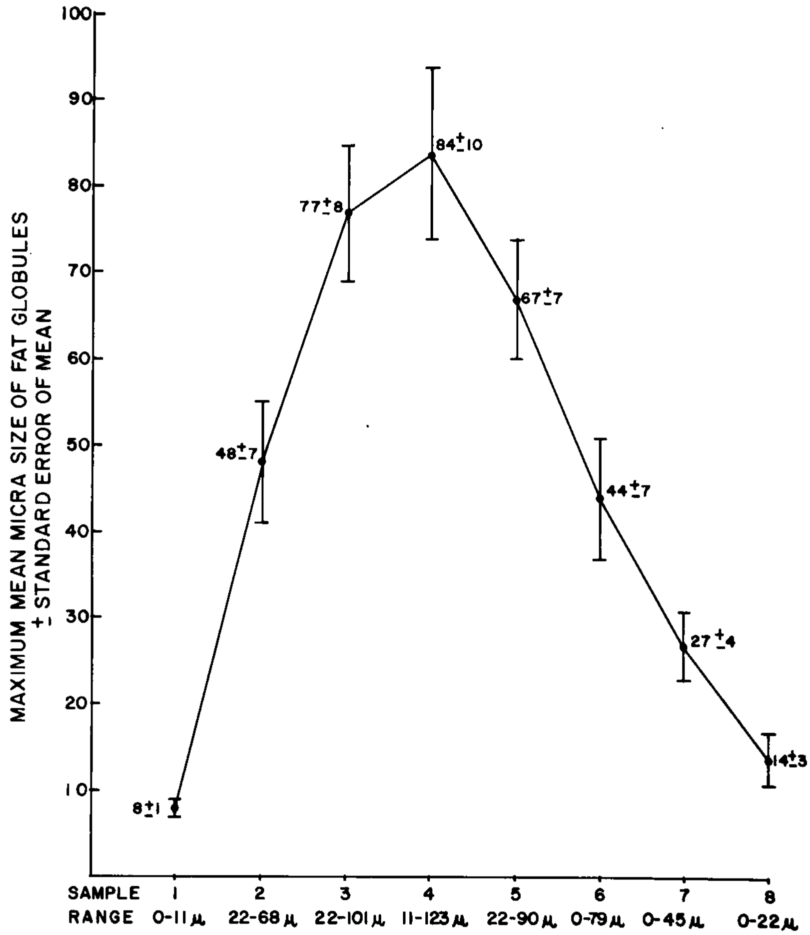

MEAN NUMBER OF FAT GLOBULES IN CUBIC MILLIMETER OF SERUM ± STANDARD ERROR OF MEAN
3000
2800
2600
2400
2200
2000
1800
1400
1200
1000
800
600
400
200
145±32
515±141
1140±362
2285±762
1657±585
897±376
535±223
349±121
1
2
3
4
5
6
7
8
SAMPLES

FIGURE 10

Maximum Globule Size Visualized in Counter per Serial Sample

Series Two


MAXIMUM MEAN MICRA SIZE OF FAT GLOBULES
± STANDARD ERROR OF MEAN
100
90
80
70
60
50
40
30
20
10
8±1
48±7
77±8
84±10
67±7
44±7
27±4
14±3
SAMPLE 1 2 3 4 5 6 7 8
RANGE 0-11μ 22-68μ 22-101μ 11-123μ 22-90μ 0-79μ 0-45μ 0-22μ

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