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Venous Thrombosis on Prosthetic Surfaces

Evolution and Blood Coagulation Studies in a Nonhuman Primate Model

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Thrombi deposited on prosthetic devices in the superior vena cava of the rhesus monkey were studied by morphologic and biochemical technics. Glass or silicone-coated glass (SCG) rings were implanted for 30 minutes to 14 days. Thrombus was deposited on the surface of each prosthetic device, and deposition was much greater and more rapid on glass surfaces than on SCG surfaces. On SCG surfaces, initial deposits consisting of single platelets, small platelet aggregates and erythrocytes were seen by scanning electron microscopy. These were followed by larger platelet aggregates, fibrin and, much later, leukocytes. Transmission electron micrographs revealed disintegration of the platelets forming aggregates and an osmiophilic deposit on the prosthetic surface. Shortened partial thromboplastin times were observed in all test animals but the sham-operated one, and therefore may be predictive of thrombus formation (Am J Pathol 75:229–242, 1974).

EXPOSURE OF BLOOD to a nonendothelial or foreign surface frequently leads to thrombosis.[1,2] The need for better understanding of thrombus-forming mechanisms is emphasized by the increased use

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of prosthetic devices in cardiovascular disease situation. Such devices may be used to replace damaged arterial segments or deformed heart valves, to function as cardiac assist devices or in any of numerous other capacities. *Ex vivo* evaluation of several possible prosthetic materials has been reported by several workers.[3–5] Still other workers have evaluated surfaces implanted as rings in large blood vessels of experimental animals. While several models have been described, the technic reported by Gott is perhaps the most widely employed.[6] In these studies rings were implanted in the canine superior vena cava, and thrombus formation in the rings was evaluated by gross inspection. Ultrastructural evaluation and correlation with hematologic parameters in the postoperative period have not been reported.

The blood coagulation, platelet aggregation and fibrinolytic systems of nonhuman primates resemble the corresponding systems in humans more closely than do those of many lower mammals.[7,8] We therefore modified previously described technics and implanted rings composed of test materials in the vascular system of the rhesus monkey rather than the dog. A glass or silicone-coated glass (SCG) ring was placed for a predetermined length of time in the superior vena cava and then removed. During the period of ring implantation, several coagulation and cellular hematologic parameters were recorded. The removed rings with attached thrombotic material were examined grossly and then ultrastructurally by two and three dimensional studies.

Materials and Methods

Nonhuman Primate Model

Seventeen young healthy male or female rhesus monkeys weighing from 3.7 to 9.4 kg were premedicated with Innovar® and subsequently given halothane anesthesia. Respiration during anesthesia was assisted manually, and a right thoracotomy was performed under sterile conditions. Test rings were implanted in the superior vena cava through an incision in the right auricle and later removed by the same route. For short-term studies (2 hours or less) the monkeys were maintained under anesthesia for the entire period. For studies of longer duration the monkeys were allowed to recover consciousness and were maintained in a postsurgical care area. For each postoperative venipuncture the animal was lightly anesthetized with Innovar. The use of drugs other than Innovar and halothane was avoided. The animals were fed Purina 25 Monkey Chow and had unrestricted access to water.

Implanted Rings

All rings were made of Pyrex glass, and some glass rings were silicone coated (G. E. Dri-Film SC-87). Rings of a size appropriate for individual venae cavae were used. The rings had internal diameters of 3 to 7 mm and were 1 to 1.5 cm

long. Glass surfaces were chosen because of their relatively poor compatibility with blood, and SCG surfaces were chosen for their relatively good compatibility. The amount of thrombus present upon each ring at the time of retrieval from the test animal was estimated macroscopically and recorded schematically (Text-figure 1).

Hematologic Studies

One control and 3 test monkeys were selected for evaluation by means of blood coagulation and other hematologic tests during the period of ring implantation. Hematocrit (Hct) determinations, leukocyte counts [7] (LC) and platelet counts [7] (PC) were done by standard methods. Procedures for determination of partial thromboplastin time [10] (PTT) tests, Stypven time [11] (ST) tests, and plasminogen and plasmin assays [12] have been described. Fibrin degradation products were determined by the staphylococcal clumping test.[13] All hematologic studies were performed on fresh blood or plasma at the Delta Regional Primate Research Center, Covington, La.

Morphologic Studies

Each implanted ring, on retrieval from the test monkey, was immediately immersed in 4/3% buffered glutaraldehyde for 1 to 2 hours. During the initial period of glutaraldehyde fixation the amount of thrombus deposited upon the ring was estimated by macroscopic inspection and recorded in a manner similar to that reported by Gott [6] (Text-figure 1). Additional procedures for fixation and process-

Interval of ring implantation		No. of animals studied	Schematic of thrombus deposition
Glass	SCG		
30 min		2	
2 hr		1	
1 day		1	
	2 hr	1	
	4 hr	2	
	8 hr	1	
	1 day	2	
	2 days	2	
	3 days	1	
	4 days	2	
	14 days	2	

TEXT-FIG 1—Macroscopic study of thrombus formation on glass and silicone-coated glass rings implanted in superior venae cavae of rhesus monkeys.

ing of specimens for scanning and transmission electron microscopy have been described.[3] A representative portion of each specimen was selected for ultrastructural study. Surface ultrastructural studies were performed with a Philips scanning electron microscope. Two dimensional ultrastructural studies were performed with a RCA EMU 3G electron microscope.

Results

Responses by flowing blood to artificial surfaces were studied temporally in 17 rhesus monkeys. Glass or silicone-coated glass (SCG) rings were placed in the superior vena cava for time intervals ranging from 30 minutes to 2 weeks and were then removed. In certain animals, several hematologic parameters were determined during the period of ring implantation. On retrieval of the rings, deposited thrombi were observed macroscopically, amount and distribution recorded, and the specimens prepared for ultrastructural study.

Hematologic Changes

Several blood coagulation and other hematologic parameters were monitored in selected animals without implanted ring (1 animal) or with an implanted ring having a silicone-coated surface (3 animals). Results of these studies are listed in Table 1. Hematocrits decreased postoperatively in all animals. In comparison with preoperative determinations, platelet counts were decreased on the first postoperative day in all animals. Recovery was variable, with prompt relative thrombocytosis in animal A. Recovery was more gradual in other animals, with all but animal C finally having thrombocytosis. Postoperative leukocytosis was noted in all animals and was least marked in the control, animal D.

Preoperative partial thromboplastin times ranged from 52 to 64 seconds. During the postoperative period these values were markedly shortened only once in each test animal. The day of PTT shortening varied, and no appreciable variation was noted in the control animal. Preoperative Stypven times ranged from 74 to 76 seconds. Following operation these values varied with no specific detectable pattern. Altered fibrinogen titers in all animals rose slightly following surgery. Plasminogen levels decreased slightly in animals B and D after surgery and then rose slowly during the postoperative period, while subjects A and C showed only a gradual rise. Assays for plasmin were negative in all cases.

Morphologic Studies

Thrombi were deposited rapidly on uncoated glass surfaces and relatively more slowly on silicone-coated surfaces. Despite this differ-

Table 1—Some Hematologic and Blood Coagulation Changes in Rhesus Monkeys with Implanted Silicone-Coated Glass Vena Cava Rings

Subject	Days vena cava ring implanted	Hct (%)	PC†	LC†	PTT‡	ST‡	Altered fibrinogen	Plasminogen (CTA units)
Implanted								
A	0*	43	314	9	52	74	1:256	0.88
	1	—	179	11	39	66	1:512	0.98
	2	45	417	19	48	68	1:512	1.10
B	0*	44	281	11	64	76	1:256	0.77
	1	42	218	17	64	88	1:512	0.68
	2	42	250	24	35	82	1:512	0.93
	3	40	405	13	64	68	—	1.14
C	0*	40	376	9	58	75	1:128	0.96
	1	37	273	30	63	64	1:512	0.97
	2	37	317	15	66	68	—	1.00
	3	33	349	14	42	37	1:512	1.29
	4	34	375	14	66	59	—	1.25
Control§								
D	0*	45	372	11	56	75	1:128	0.97
	1	—	297	17	62	83	1:256	0.75
	2	43	244	17	60	83	1:512	0.72
	3	43	314	13	60	77	—	0.96
	4	45	488	12	57	74	1:512	1.03

* Blood was drawn after induction of anesthesia with Innovar and 20 to 30 minutes before operation. For all subsequent venipunctures each animal was anesthetized with Innovar.
† PC = platelet count; LC = leukocyte count (× 1000/cu mm).
‡ PTT = partial thromboplastin time; ST = stypven time (sec).
§ Same operative procedure as above, but no ring was implanted.

ence, trace amounts of thrombus were deposited early on both types of surfaces. Degree of thrombosis was evaluated first by gross visual inspection and then more extensively by ultrastructural technics.

Macroscopic Observations

Grossly evident thrombi appeared on uncoated surfaces of glass rings much more rapidly than on silicone-coated surfaces. Thrombi which were observed macroscopically are illustrated schematically in Text-figure 1. By this technic faint traces of thrombi were evident on glass rings removed after 30 minutes implantation, while gross thrombi were progressively more in evidence at the end of 2 hours and 1 day.

In contrast, only trace thrombi were irregularly in evidence by gross inspection on silicone-coated rings which were in place for periods ranging from 2 hours to 3 days. After 4 days in 1 of 2 animals and in each of 2 animals at the end of 14 days, large and extensive thrombi were finally observed on SCG rings.

Ultrastructural Studies

Trace amounts of deposited thrombus, recognized macroscopically as faintly roughened or dull areas on the glass or SCG surfaces, were examined three dimensionally with the scanning electron microscope. Trace thrombus was found on a glass ring exposed to flowing venous blood for 30 minutes and on SCG rings removed after implantation for 2 or 8 hours, or 1, 2 or 4 days. Larger thrombi were examined both by scanning electron microscopy and in two dimensions with the transmission electron microscope.

Uncoated Glass Ring Prostheses

Thrombus was widely though thinly deposited on the glass surface at the end of 30 minutes of implantation. The thrombus was composed of platelet masses and erythrocytes enmeshed in many fibrin strands (Figure 1). In some aggregates, platelets extended numerous slender elongated undulating pseudopods outward from the aggregate mass (Figure 2). By transmission electron microscopy, numerous aggregates of platelets were observed, some being very close to the glass surface (Figure 3). Many such aggregates were in an advanced stage of thrombocytorrhexis. Fibrin was variable, being prominent in and about some aggregates (Figures 1 and 3) and inapparent in others (Figure 2). A rare single leukocyte (not illustrated) was observed at this time.

Silicone-Coated Glass Rings Implanted Up to 1 Day

A SCG ring implanted for 2 hours had on its surface only very thinly scattered erythrocytes and platelets (Figure 4). Platelets were single or in small aggregates of two or three cells. Their shapes were frequently bizarre, with both blunt and slender projections. Fibrin was not observed in the 2-hour specimen.

In the ring implanted for 8 hours, multiple minute thrombi were observed on the SCG surface. These consisted of aggregates of perhaps 10 to 15 platelets with a few erythrocytes and an occasional leukocyte (Figure 5). Leukocytes were first observed in the 8-hour specimen. An occasional suggestion of fibrin was observed in the form of a fibrillar structure such as partly overlies the erythrocyte to the right in Figure 5.

At the end of 1 day of implantation, thrombus deposition is much more evident on the SCG surface. There is moderate variation in distribution (Figure 6), with clear areas alternating with areas of moderately or marked deposition. Individual cell aggregates are similar to those in the 8-hour sample, also containing platelets, leukocytes and erythrocytes (see Figure 5). In a transmission electron micrograph of

one of the aggregates a leukocyte is seen adjacent to the prosthetic surface (Figure 7). A thin osmiophilic layer separates the leukocyte from the artificial surface.

Silicone-Coated Glass Rings Implanted Longer Than 1 Day

At the end of 2 days implantation the degree of the thrombosis was still greater than in earlier samples and was moderately evenly distributed on the siliconized surface (Figure 8). Among many small aggregates were several large aggregates of cells. As in previous samples these were composed of several cell types, including platelets, erythrocytes and leukocytes (Figure 9). Leukocytes were proportionately greater in numbers than they were in aggregates of earlier samples although platelets continued to be the major cell comprising the aggregates. The several slender projections which extend outward from numerous aggregates probably represent platelet pseudopods (see Figure 8). As seen in transmission electron micrographs, platelets with central organelle apposition and disintegration, indicating individual cell thrombocytorrhexis, were enmeshed in fibrin fibrils (Figure 10). Some were immediately adjacent to the osmiophilic layer at the siliconized artificial surface. Above these platelets were several erythrocytes.

On the margins of a SCG ring left implanted for 4 days, heavy thrombus deposits were observed; they are illustrated in a surface ultrastructural view (Figure 11). The thrombus was composed of cells similar to those seen in earlier samples. Fibrin fibrils were numerous.

Discussion

A nonhuman primate model has been used to study *in vivo* responses by blood to foreign surfaces. In addition to providing opportunity for study of thrombus evolution, two surfaces markedly different as to their thrombogenicity have been compared. It seems likely that this model should reflect compatibility of human blood to foreign surfaces more nearly than a model using a nonprimate animal such as the dog or a ruminant. This model is adaptable for the study of any material which could be fabricated in tubular form or which could be used to coat another material in tubular form. Additionally, this model could be utilized in testing the relative efficacy of antithrombotic agents.

In the study reported here two surfaces were selected for comparison of their thrombogenicity. One of the surfaces, Pyrex® glass, was chosen for its well-known poor compatibility *in vitro* and hence its expected high thrombogenicity *in vivo*. The other surface, silicone-coated glass,

was chosen for contrast because of its relatively high compatibility with blood and therefore its relatively low thrombogenicity.

Compatibility of each of the two surfaces was followed in a time sequence manner by removing the prosthetic ring for morphologic study at varying time intervals. During the time of ring implantation several hematologic parameters were observed in several test animals and a control or sham-operated animal was similarly observed for comparison.

Hematologic parameters were followed in the test animals in hope of identifying one or more tests which might be predictive of thrombus formation. Partial thromboplastin times were markedly shortened once in each test animal, while shortening of the PTT was not demonstrated in the sham-operated animal. This shortening of the PTT in test animals may therefore reflect active deposition of thrombus. Decrease in platelet counts, observed early in the postoperative course in all animals, probably reflects active postoperative hemostasis rather than thrombus deposition on the prosthetic surface. Similar postoperative fluctuations have been reported by others.[14] Other parameters failed to follow a consistent pattern which might be interpreted as reflecting thrombosis.

Thrombus deposition on the two foreign surfaces used in this study was both similar and dissimilar. Similarities included the deposition of thrombi and the order in which both cellular and noncellular blood components were deposited. The principal dissimilarity was a difference in the rate of thrombus deposition. On both the noncoated and silicone-coated glass surfaces there was early deposition of some thrombus, but this was much greater on the noncoated surface as compared with the coated one. The thrombus deposited on glass by the end of 30 minutes was both widespread and considerable in amount. Lying directly on the glass surface there was a thin layer of osmiophilic material (Figure 3). Adjacent to this were masses of aggregated platelets and fibrin (Figures 1–3) similar to those previously described in clotting platelet-rich plasma during thrombocytorrhexis and early lysis.[15] Also above the osmiophilic layer were erythrocytes, frequently among intertwining fibrils of fibrin (Figure 1). Some of the platelet aggregates were compact with many markedly elongated, undulating pseudopods (Figure 2). At this time a rare leukocyte was observed.

In contrast with this pattern of a complex thrombus deposited early on the uncoated glass surface, the rate of thrombus deposition is much more gradual on the silicone-coated glass surface. After 2 hours implantation of a SCG ring there were adherent to the surface only scattered erythrocytes and platelets, the latter in singles or pairs (Fig-

ure 4). Despite extensive examination, neither fibrin nor leukocytes were observed.

On siliconized surfaces implanted for longer periods of time the amount, quality and complexity of thrombus deposition gradually changed. An occasional leukocyte was first seen after 8 hours implantation, and at that time a suggestion of fibrin formation was observed by scanning electron microscopy (Figure 5).

By the end of 1 day, thrombus was much more in evidence though irregularly deposited. After 2 days larger, more complex aggregates were seen. These were composed of masses of aggregated platelets plus erythrocytes and leukocytes (Figures 8 and 9). Although the role of these cells in thrombus formation is not certain, the presence of intact leukocytic granules suggests that lytic enzymes have not been released. In at least some aggregates, thrombocytorrhexis was in progress and fibrin fibrils were present about platelets and other cells (Figure 10). A possible role for the leukocytes in these thrombi may be phagocytosis of platelet remnants undergoing self-destruction.[15] Rings implanted for still longer times exhibited much more extensive thrombosis.

These experiments have demonstrated the usefulness of a nonhuman primate model for evaluating surfaces of varying thrombogenicity and for observing evolution of the thrombus on a surface exposed to slowly flowing venous blood. The much slower rate of thrombus formation on the prosthetic surface of lower thrombogenicity has allowed detailed demonstration of progressive complexity of the thrombus. Initially there were a few single platelets or aggregates plus a few erythrocytes but without fibrin (Figure 3). Much later a few strands of fibrin and an occasional leukocyte were added (Figure 5), and then platelet disintegration occurred and leukocytes in larger numbers appeared (Figures 8–10). Finally, a much larger thrombus was composed of similar elements in greater numbers.

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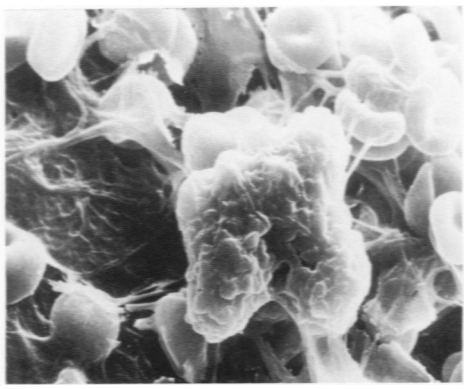
Legends for Figures

Fig 1—A scanning electron micrograph (SEM) of thrombus deposited on a glass ring implanted for 30 minutes in the superior vena cava of a rhesus monkey. In the center there is a platelet aggregate composed of approximately 15 or 20 platelets. Pseudopods of these platelets are short and blunt. Adjacent to the aggregate are numerous erythrocytes and many fibrin fibrils which overlie erythrocyes and the glass surface. Fibrin on the glass surface is seen best on the left (× 835).

Fig 2—SEM of another platelet aggregate from the same sample as Figure 1, a glass ring implanted for 30 minutes. This aggregate is composed of six or eight platelets and has numerous long, slender and undulating pseudopods which extend outward from the platelets at multiple sites and in many directions. Several erythrocytes lie adjacent to the platelets, above and to the right. Fibrin fibrils are in the background in the upper right but are not identified in the platelet aggregate (× 4180).

Fig 3—A transmission electron migrograph (TEM) of a mass of platelets and fibrin immediately adjacent to the osmiophilic layer which was in turn adjacent to the glass surface (*arrow*) which had been implanted for 30 minutes. Platelets are undergoing disintegration and are in a state of thrombocytorrhexis and early lysis. Organelles, except for an occasional mitochondrion near the left margin, are not identifiable (× 16,000).

Fig 4—SEM of a representative area of a silicone-coated glass (SCG) ring implanted for 2 hours. Erythrocytes are sparsely distributed. Scattered individual platelets and aggregates composed of two or three platelets are observed. The platelets have numerous projections, some stubby and some long and slender. Fibrin is not observed (× 2470).



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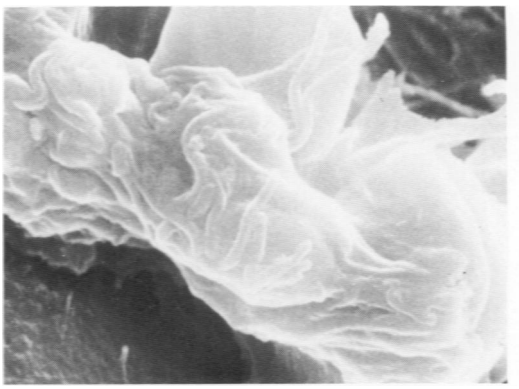

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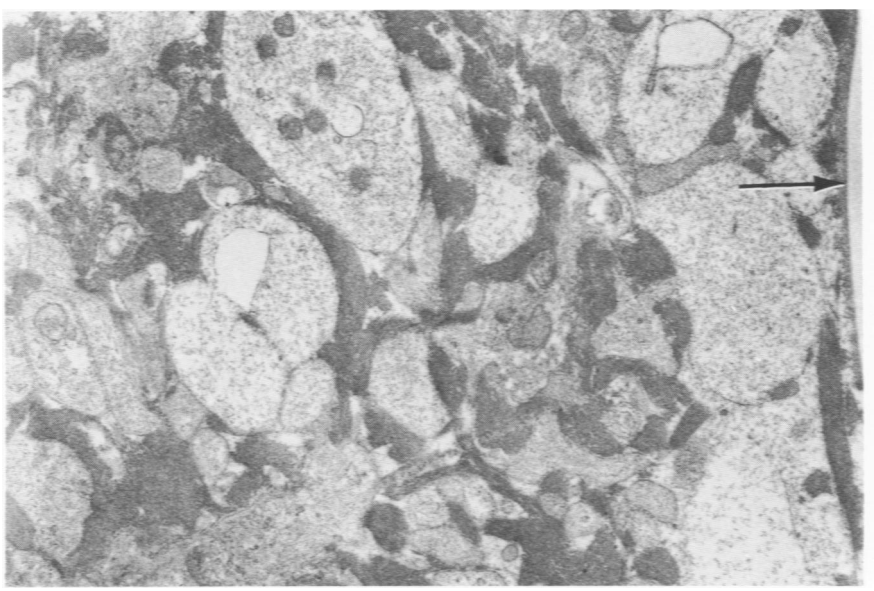

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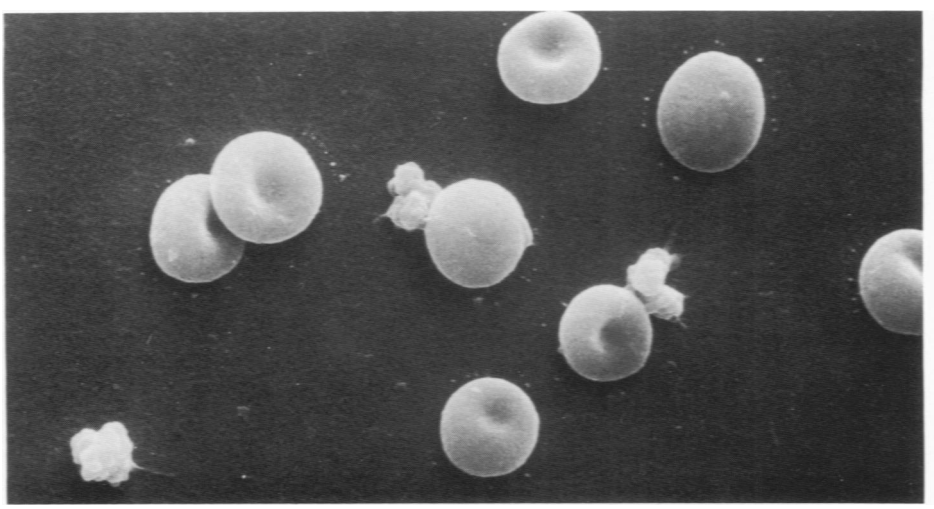

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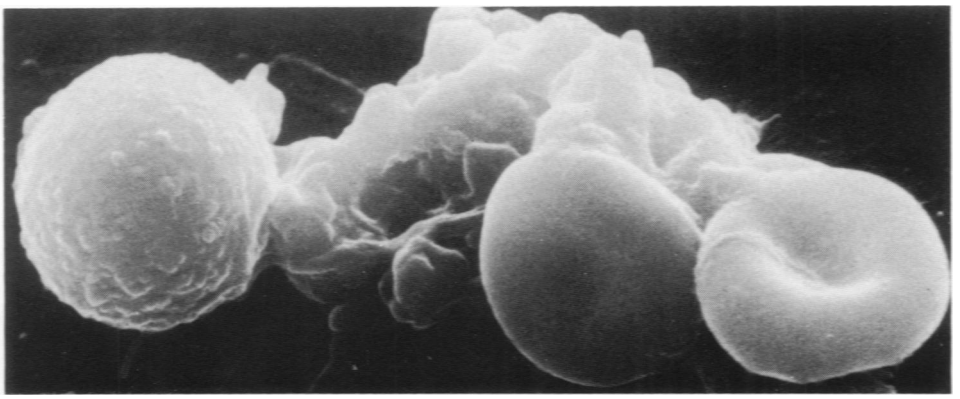

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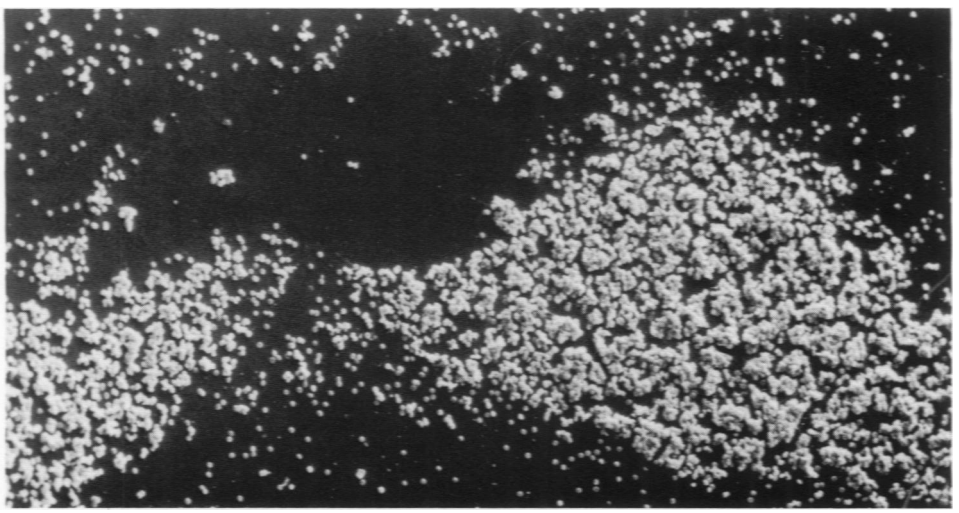

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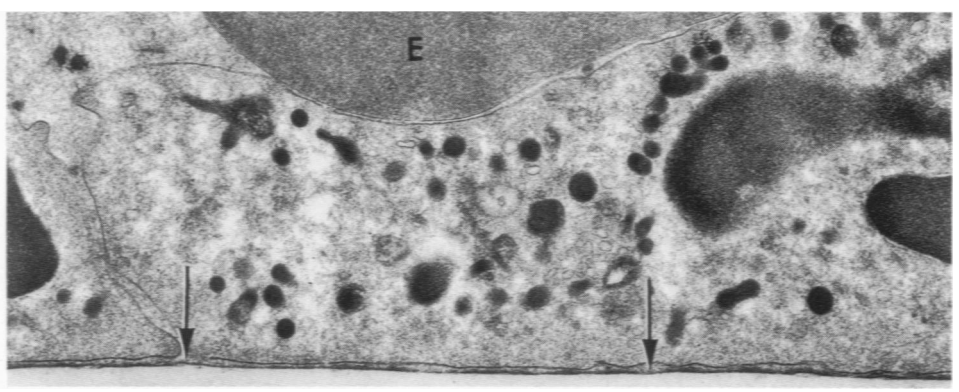
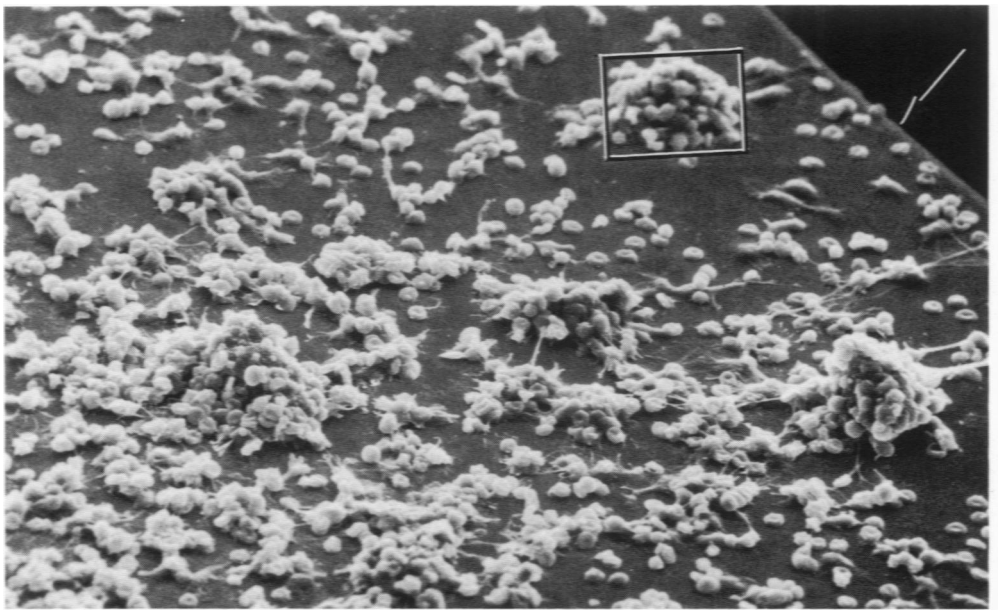


Fig 5—SEM of a platelet aggregate with adjacent cells of other types, lying on the surface of a SCG ring implanted for 8 hours. The aggregate (*center*) is composed of 10 or more platelets. A leukocyte is seen to the left and 2 erythrocytes are on the right. Elongated fibrillar material is occasionally seen, such as in the concavity and over the convexity of the erythrocyte on the right. This may represent early fibrin deposition (× 6000).
Fig 6—SEM of the surface of a SCG ring implanted in the superior vena cava for one day. Thrombus was irregularly deposited, varying from areas which are clear and free of thrombus to areas of moderately dense deposit. In more dense areas the separation of groups of cells by irregular spaces is a drying artifact of specimen preparation (× 63). **Fig 7**—A TEM of thrombus of the SCG ring left implanted for 1 day. This view illustrates parts of two leukocytes spread on and closely apposed to the osmiophilic dense zone (*arrows*) which is deposited directly on the SCG surface. Lying directly above one of the leukocytes is an erythrocyte (*E*) (× 13,800).



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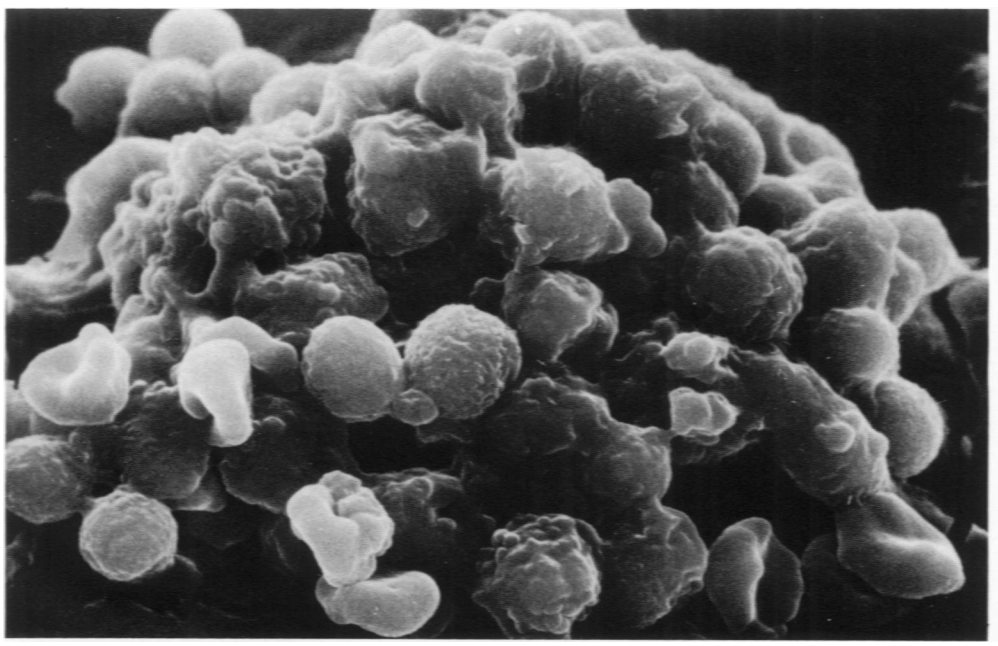

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Fig 8—SEM of a SCG ring implanted in the superior vena cava of a rhesus monkey for 2 days. In this area of rather dense thrombus deposit are numerous small aggregates composed predominately of erythrocytes and platelets. In addition there are multiple larger aggregates which measure up to 60 μ in diameter at their bases. The large aggregates were not observed immediately adjacent to the edge of the ring, which is seen in the upper right (*arrow*). They were no closer than approximately 25 μ. The aggregate in the inset in the upper right constitutes Figure 9 (× 410). **Fig 9**—This aggregate is from the inset of Figure 8. It is a larger, more complex aggregate than those seen in earlier samples. There are multiple small platelet aggregates within the larger aggregate (*long arrows*) plus erythrocytes and leukocytes (*short arrows*). Fibrin is not observed in this area (× 2580).

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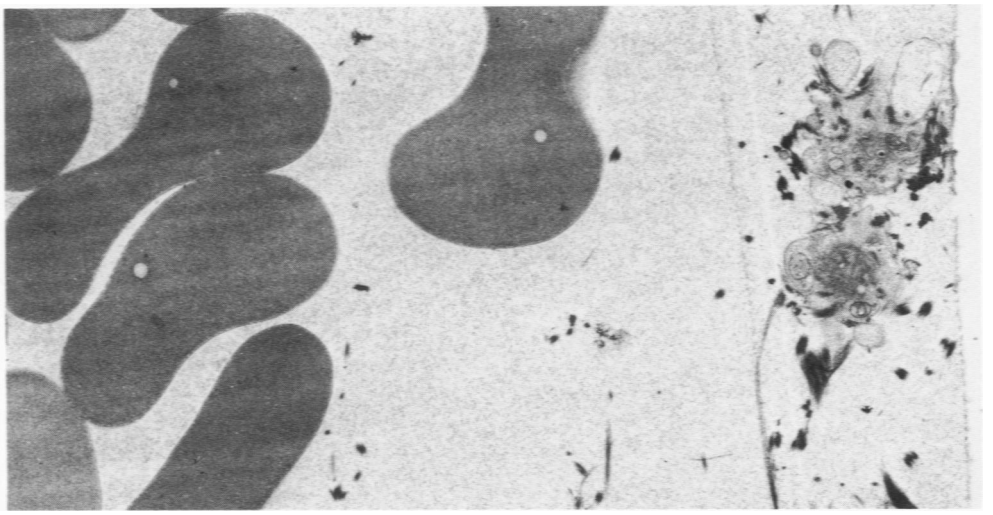

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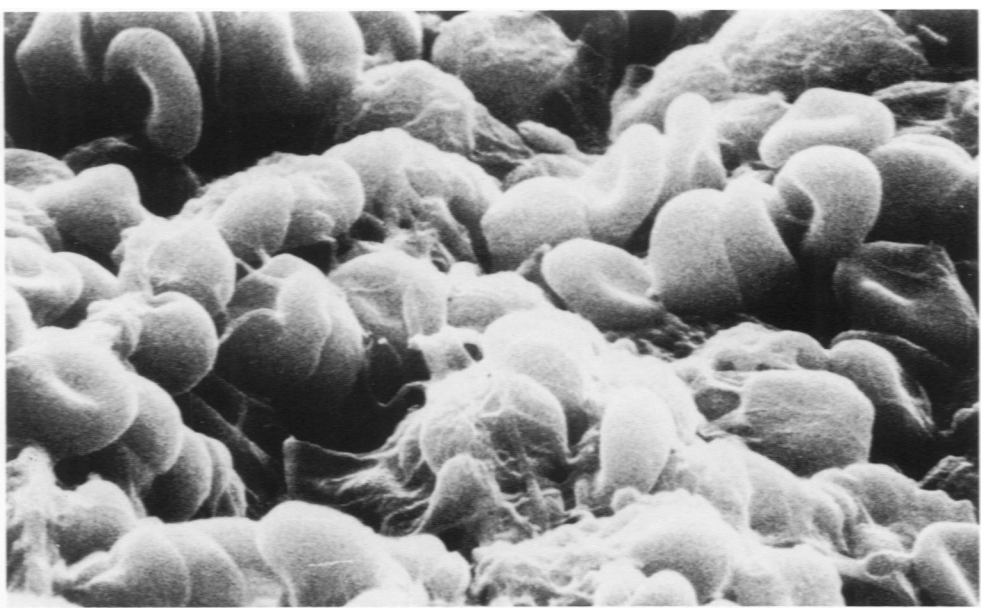

Fig 10—A TEM of another SCG ring implanted in the superior vena cava for 2 days. In this micrograph the osmiophilic layer deposited on the SCG surface is vertically oriented at the right. Immediately adjacent is a small aggregate of three or more platelets and fibrin. Platelet organelles have disintegrated, indicating early rhexis, but intact plasma membranes suggest that lysis has not begun. Erythrocytes are in a rather thick layer beginning about 6 μ above the osmiophilic layer. A few fibrin fibrils are seen in spaces around and between erythrocytes (× 6340). **Fig 11**—SEM of the surface of a large thrombus deposited on a SCG ring implanted in the rhesus monkey superior vena cava for 4 days. There are many erythrocytes and fibrin fibrils overlying the surface of the thrombus. Platelets are not specifically identified in this micrograph (× 3590).