Clearance of microparticulate fibrin by the reticuloendothelial system has been long recognized as a defense mechanism against intravascular fibrin deposition (1, 2). In general this has been assumed to be part of the relatively nonspecific phagocytic process whereby the reticuloendothelial system removes other microparticulate material such as bacteria, from the circulation. Numerous in vitro studies (3-7) have documented the fact that before formation of particulate fibrin, fibrin may exist in a soluble form, generally when in a soluble complex with fibrinogen, and/or fibrin degradation products (5-7). Recently we have demonstrated that soluble macromolecular complexes consisting of known ratios of fibrinogen and fibrin which were formed in vitro, remain soluble when injected into rabbits (7). These complexes also had impaired clearance from blood during reticuloendothelial system blockade with Thorotrast. In nonblockaded animals, the blood t½ of the fibrinogen/fibrin complex was less than 1 h. The results indicated that in part reticuloendothelial system uptake of fibrin depended on specific binding of soluble fibrin, before microparticle formation and phagocytosis. Specificity for fibrin was suggested, because in the same Thorotrast model we were unable to demonstrate impaired clearance of fibrinogen degradation product D (8), and intact fibrinogen had a normal blood t½. Removal of soluble fibrinogen/fibrin complexes is of pathophysiological significance because of the clear, frequent clinical association of these complexes with intravascular coagulation (9-12), in contrast to the very rare demonstration of circulating microparticulate fibrin.

To explore further the soluble fibrin-reticuloendothelial system interaction, and a possible surface receptor, in the present report, isolated peritoneal macrophages have been studied for their ability to bind soluble fibrin, fibrinogen, and other fibrinogen derivatives.

Materials and Methods

Fibrinogen and Derivatives. Human fibrinogen fraction I-4 was purified by the method of Blomback and Blomback (13) to ≥95% clottability. Fibrinogen was labeled with 125I or 131I by the method of McFarlane (14) with ≤0.5 atoms iodine/mole fibrinogen and ≥94% radioactive clottability. The radiolabeled fibrinogen (F) was converted to fibrin (f) by thrombin and the resultant clot

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Abbreviations used in this paper: CIG, cold-insoluble globulin; CTA, Committee on Thrombolytic Agents; f, soluble fibrin; F, fibrinogen; HBSS, Hanks’ balanced salt solution; PMNs, polymorphonuclear leukocytes; SBTI, soy bean trypsin inhibitor.
was redissolved in 0.27 M Tris HCl, 0.03 M Tris-acetate buffer, pH 5.3, as previously described (7).

In some instances, the soluble fibrin was added to fibrinogen to form fibrin/fibrinogen complexes (f/F). These complexes are large polymers which emerge at the void volume on Sepharose 4B and have a Ve/Vo of 1.17 on Sepharose 2B. A double labeled \(^{125}\text{I}-f/^{131}\text{I}-F\) preparation illustrates that both F and f are present in the void volume complex (Fig. 1). A second peak contains some noncomplexed F and a small variable amount of f. The second peak corresponds to the Ve of F alone. \(^{131}\text{I}-F\) alone emerges at the void volume with a small amount in the F position (7). Thrombin neutralization was accomplished with 10 \(-2\) M diisopropylfluorophosphate. In some instances f was formed in the presence of Ca\(^{++}\) so as to obtain cross-linked f. "Late" crude plasmin digests of F (f degradation products) were prepared by addition of 30 U streptokinase to 24 mg F in 0.1 M Tris-C1 buffer, pH 8.4, and incubation at 37°C for 18 h. Late fibrin degradation products were similarly prepared except that thrombin was added just before the streptokinas. For "early" fibrin degradation products, soy bean trypsin inhibitor (SBTI) was added at the time of clot dissolution.

Macrophages. Guinea pig peritoneal macrophages were harvested 3 days after intraperitoneal injection of 20 ml Marcol 52 (Humble Oil & Refining Co., Houston, Texas) (15). The cell suspension was washed and resuspended in RPMI 1640, with 10% fetal calf serum. The cells were incubated in glass Petri dishes for 18 h at 37°C in 5% CO\(_2\). The contaminating lymphocytes were poured off, and the adherent macrophages washed with Hanks' balanced salt solution (HBSS). The macrophages were harvested with a rubber policeman, washed, and resuspended in HBSS. Resuspended macrophages were \(\approx 90\%\) viable by trypan blue exclusion and \(\approx 90\%\) of the cells phagocytized yeast particles.

Other Cell Types. Washed guinea pig lymphocyte suspensions were prepared from the nonadherent cells after overnight culture of the Marcol-induced peritoneal exudates. Cultures of human skin fibroblasts were kindly supplied by Dr. Nancy Baenziger. Guinea pig peritoneal polymorphonuclear leukocytes (PMNs) were harvested 18 h after injection of 20 ml of 6% caseinate (15). The exudates contained \(\approx 96\%\) PMNs.

Experimental. For most experiments \(1.5 \times 10^6\) cells were suspended in HBSS or 0.007 M NaH\(_2\)PO\(_4\), 0.15 M NaCl, pH 7.4 buffer, in Falcon 12 \(\times\) 75 mm tubes (Falcon Plastics, Div. of BioQuest, Oxnard, Calif.) Cell metabolism was inhibited with either 1 \(\times 10^{-9}\) M NaF and 2 \(\times 10^{-4}\) M KCN or 20 mM 2-deoxyglucose and 1 mg/ml sodium azide. Varying amounts of \(^{125}\text{I}-f\) or \(^{131}\text{I}-F\) were then added and the total radioactivity measured. Unless so indicated, incubations were for 45 min. 22°C was usually employed because it was desirable to avoid enhanced metabolic activity at 37°C, yet f is poorly soluble at 4°C. The experiments comparing macrophages, lymphocytes, fibroblasts, and erythrocytes were at 37°C because it is known that f/F will bind soluble fibroblast surface antigen, or cold-insoluble globulin (CIG), at low temperatures, but not at 37°C. After incubation, the cells were centrifuged for 5 min at 2,500 g and 22°C, and the supernate removed. Two washes of the cells with HBSS were performed. Preliminary studies demonstrated that no additional radioactivity was removed by added washes. The cell-bound radioactivity was determined in a Packard dual channel gamma counter (Packard Instrument Co., Inc., Downers Grove, Ill.). In instances when both \(^{125}\text{I}\) and \(^{131}\text{I}\) were used, the \(^{125}\text{I}\) counts were corrected for the scatter of \(^{131}\text{I}\) counts into the \(^{125}\text{I}\) channel. Blank controls with \(^{125}\text{I}-f\) or \(^{131}\text{I}-f/F\) but without cells were also run.
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Centrifugation of ≤20 μg 125I-f or ≤500 μg 125I-f/F in HBSS at 7-10,000 g for 20 min without cells, showed neither a precipitate nor significant change in the specific activity of the solution. This is in keeping with previous data (7) that the f/F complex remains both soluble, and as a complex, in the blood of animals after injection of f/F. All tests were run in duplicate or triplicate. The amount bound was usually expressed as micrograms per 10⁶ cells, and was corrected for the blank controls, which did not exceed 5% of the cell-bound values.

Specificity. The specificity of binding was assessed first by the effect of prior incubation of the cells with nonradioactive f and F. Secondly the interaction with the IgG receptor was assessed for both IgG and immune complexes. For immune complexes, rat IgE and goat anti-IgE were kindly supplied by Dr. A. Kulczycki (16). A 25-fold range of IgE was used so as to span the previously determined range of equivalence. The antisera concentration was 0.15 ml in 0.5 ml final test vol. The same amount of human IgG was used for IgG alone. Human IgG was prepared by ion exchange chromatography and was immunoelectrophoretically homogeneous using anti-human IgG and anti-whole human sera (Behring Diagnostics, American Hoechst Corp., Somerville, N. J.). Because of the high protein concentration, a control with a similar amount of human serum albumin (Hyland Laboratories, Los Angeles, Calif.) was run.

Effects of Trypsin and Plasmin

Pretreatment. Cells were preincubated with either 0.25 mg/ml trypsin (Sigma Chemical Co., St. Louis, Mo.) and 0.4 mg/ml ribonuclease (Worthington Biochemical Corp., Freehold, N. J.), or 3 Committee on Thrombolytic Agents (CTA) U plasmin (17) for 30 min at 37°C. 0.5 mg/ml SBTI was added, the supernate removed, and the cells washed twice and resuspended for addition of labeled f or f/F.

Postfibrin Exposure. In other experiments, after incubation with radiolabeled f or f/F, the cells were centrifuged, washed, and the bound radioactivity counted. HBSS was readded with 1 mg/ml of trypsin or 3 CTA U plasmin for 20 min at 37°C. The cells were recentrifuged, washed, and radioactivity recounted.

Effect of Divalent Cations. The macrophages were suspended in HBSS solution with metabolic inhibitors, without Ca ++ or Mg ++, and 125I-f added. Other tubes had 0.9 mM CaC1₂ or 0.5 mM MgCl₂ and 0.4 mM MgSO₄ added before addition of the 125I-f. The entire experiment was run with both cross-linked and noncross-linked 125I-f. Experiments with noncross-linked f and Ca ++ utilized 10⁻³ M iodacetamide to inhibit any trace F XIII activity.

Results

Binding of Derivatives (Table I). In the standard incubations both f and f/F complexes were bound to the macrophages. Intact F, late F degradation products, and late f degradation products were bound in much smaller amounts. When early 125I-f degradation products were mixed with F before addition to the tubes, 1.5 μg early 125I-f degradation products was bound per 10⁶ cells. No such enhanced binding was observed when F and early F degradation products were mixed together before addition to the cells. Binding was progressive until 30 min and remained essentially constant thereafter (Table II).

Localization of 125I-f. To differentiate between membrane-bound and intracellular 125I-f, after incubation with 125I-f, cells were washed, counted, and reincubated with plasmin or trypsin (Table III a). Essentially, all the cell-bound radioactivity was removed, by either enzyme.

Binding Sensitivity to Pretreatment with Plasmin and Trypsin (Table III b). Cells pretreated with plasmin and trypsin retained 125I-f binding capability. 125I-f/F demonstrated the same binding characteristics as 125I-f alone.

Concentration Dependence of f and f/F Binding. To examine the effect of higher concentrations of f, f/F was used because of the marginal solubility of f alone in concentrations above 20 μg/ml. Increasing concentrations of f/F reached a plateau at approximately 5.4 μg or 3.6 μg f/10⁶ macrophages (Fig. 2). Scat-
TABLE I

Macrophage Binding of F Derivatives

| Derivative                      | µg protein bound/10⁶ cells* |
|--------------------------------|------------------------------|
| ¹²⁵I-F                         | 0.05 ± 0.025                 |
| Soluble ¹²⁵I-f                 | 1.7 ± 0.3                    |
| ¹²⁵I-f/F complex               | 1.4 ± 0.2                    |
| Late ¹²⁵I-FDP†                 | 0.09 ± 0.01                  |
| Late ¹²⁵I-fdp†                 | 0.10 ± 0.03                  |
| Early ¹²⁵I-fdp and F           | 1.5 ± 0.2                    |
| Late ¹²⁵I-fdp and F            | 0.15§                        |
| Early ¹²⁵I-FDP and F           | 0.06§                        |
| Late ¹²⁵I-FDP and F            | 0.07§                        |

* Mean ± SD of four experiments.
† FDP, F degradation products; fdp, f degradation products.
§ Two experiments.

TABLE II

Micrograms of f Bound vs. Time

| Time (min) | µg f bound/10⁶ cells |
|------------|---------------------|
| 5          | 0.24                |
| 10         | 0.56                |
| 20         | 1.28                |
| 30         | 1.52                |
| 45         | 1.70                |
| 90         | 1.65                |
| 120        | 1.67                |
| 180        | 1.70                |

TABLE III

Effect of Plasmin and Trypsin

a. Plasmin or trypsin added after ¹²⁵I-f binding

|                      | µg ¹²⁵I-F bound* |
|----------------------|-----------------|
| Pre-enzyme           | 1.3 ± 0.2       |
| Post-trypsin         | 0.12 ± 0.07     |
| Post-plasmin         | 0.17 ± 0.06     |

b. Plasmin or trypsin treatment of cells before ¹²⁵I

|                      | µg ¹²⁵I-F bound* |
|----------------------|-----------------|
| Untreated cells      | 1.6 ± 0.3       |
| Trypsin treated cells| 1.4 ± 0.2       |
| Plasmin treated cells| 1.5 ± 0.2       |

* Mean and ± 1 SD for three experiments.

Further analysis of the data from experiments with two different macrophage preparations, indicated an average of 1.15 × 10⁻¹⁷ mol or 6.92 × 10⁶ molecules bound per macrophage (Fig. 3). Because both soluble f and f/F consist of molecular aggregates or polymers, the number of binding sites per cell is probably less. Calculation of the number of sites would require accurate molecular size data for the complexes. The large size of the complexes, and the known anomalous behavior of F on gel chromatography makes such size estimates unreliable.
Specific Binding of Soluble Fibrin to Macrophages

Fig. 2. Uptake of \(^{125}\)I-f with increasing amounts of \(^{125}\)I-I/F. I/F values are micrograms f per tube; f/F ratio was 1:5.

![Graph showing uptake of \(^{125}\)I-f with increasing amounts of \(^{125}\)I-I/F.](image)

Fig. 3. Scatchard analysis of moles \(^{125}\)I-f bound with increasing concentrations. \(^{125}\)I-f was in a \(^{125}\)I-I/F complex. Symbols (©, △) represent two separate sets of experiments. r/c, bound per unbound \(\times 10^2\).

![Graph showing Scatchard analysis of moles \(^{125}\)I-f bound with increasing concentrations.](image)

**Reversibility and Displacement.** With an incubation of 1 µg f with 1.5 \(\times\) 10\(^6\) cells for 45 min, 14% (0.14 µg) was bound. Subsequent dilution to 10 ml with addition of 50 µg nonradiolabeled f and reincubation for 45 min failed to displace any \(^{125}\)I-f. Similar experiments with ratios of 10-800:1 of "cold"; \(^{125}\)I-f and incubation for up to 180 min, all failed to demonstrate significant displacement. Prolonged incubation of cells with \(^{125}\)I-f alone did not show either significant further uptake after 45 min, or release of radioactivity. Displacement only occurred in three experiments with cold f; \(^{125}\)I-f ratios of 500:1 and a 20 h incubation period. 31 ± 10% of the cell-bound radioactivity was released. In contrast cells incubated without metabolic inhibitors showed sustained increases in radioactivity (Fig. 4). After overnight incubation without inhibitors,
Fro. Percent uptake of $^{125}$I-f by macrophages with (O) and without (●) metabolic inhibitors.

![Graph showing percent uptake of $^{125}$I-f by macrophages with and without metabolic inhibitors.]

**Table IV**

| Interaction of IgG, Soluble f, and Macrophages |
|-----------------------------------------------|
| Amount of rat IgE | % Inhibition of $^{125}$I-f binding |
|-------------------|-----------------------------------|
| 1. Albumin (6 mg/tube) | — | 21 |
| 2. Human IgG (1 mg/tube) | — | 17 |
| 3. Goat anti-rat IgE (150 μl) | — | 19 |
| 4. Immune complex | 0.0055 | 24 |
| 5. Immune complex | 0.0275 | 14 |
| 6. Immune complex | 0.1375 | 19 |

Incubation mixture included 1.5 × 10⁶ cells and 10 μg $^{125}$I-f. Tubes 3–6 had 0.15 ml of undiluted goat antisera added per tube. The amount bound with $^{125}$I-f and cells alone was considered 100%. The results are the average of three experiments with albumin and two experiments with the others.

11% of the unbound $^{125}$I was TCA soluble, indicating cellular proteolysis of $^{125}$I-f with release of free $^{125}$I.

**Specificity.** Prior incubation of cells with 100 μg nonradioactive f/F reduced uptake of 10 μg $^{125}$I-f by 71 ± 4% in three experiments. Preincubation with a 10-fold excess of F failed to inhibit uptake of $^{125}$I-f. Immune complexes and IgG alone inhibited uptake by 14–24% (Table IV). A similar decrease was seen with albumin. The modest nature of the decreased uptake in light of the 200- and 3,000-fold molar excesses of IgG and albumin suggests the effect was nonspecific.

The f uptake with albumin (1.48 μg/10⁶ cells) may represent a physiological state, more comparable to in vivo conditions, than with HBSS alone.

**Effect of Divalent Cations (Table V).** When the $^{125}$I-f uptake was tested in Hanks' solution without Ca⁺⁺ or Mg⁺⁺, negligible uptake occurred. Addition of Ca⁺⁺ alone restored f binding, whereas Mg⁺⁺ alone had no effect. The effect of Ca⁺⁺ was present with both cross-linked fibrin and noncross-linked f.

**Other Cell Types.** A limited number of studies were performed with PMNs. The same enhanced binding of f vs. F was found as with the macrophages. Substantially greater amounts of f were bound to PMNs as compared with macrophages. In the presence of 10 μg f and NaF and KCN, 4.9 ± 0.4 μg $^{125}$I-f bound/10⁶ cells in five experiments. Lymphocytes, fibroblasts, and erythrocytes bound relatively little $^{125}$I-f/F, as compared with macrophages and PMNs. The lymphocytes and fibroblasts bound approximately as much F as f (Table VI).
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Table V
Effect of Cross-Linking and Divalent Cations on Binding

|                        | µg  |
|------------------------|-----|
| Cross-linked f with Ca ++ | 1.24|
| Cross-linked f without Ca ++ | 0.07|
| Noncross-linked f with Ca ++ | 1.50|
| Noncross-linked f without Ca ++ | 0.09|
| Noncross-linked f without Ca ++ with Mg ++ | 0.06|

Table VI
Comparative Binding of f to Various Cells

| Cells         | µg bound/10⁶ cells |
|---------------|-------------------|
|               | ¹²⁵I-f | ¹²⁵I-f/F |
| Macrophages   | 1.8   | 0.05    |
| Lymphocytes   | 0.17  | 0.08    |
| Fibroblasts   | 0.19  | 0.18    |
| Erythrocytes  | 0.09  | 0.03    |

Macrophage, lymphocyte, and erythrocyte values are the means of three experiments. Fibroblast results are means of two experiments.

Discussion

The cellular uptake of soluble f and f/F complexes described above would appear to be the result of cell surface binding. Intracellular ingestion was prevented by use of metabolic inhibitors. Subsequent removal of the cell-bound f by trypsin and plasmin was added evidence that the f was on the outside of the cells. A major concern was the possibility that the f and f/F were artifactually precipitated or polymerized with the cells. The low binding in the blank controls and other cell types except PMNs (Table VI), and the unchanged specific radioactivity of ¹²⁵I-f and ¹²⁵I-f/F in HBSS after centrifugation, are evidence against precipitation. Additionally, saturation of uptake above 300 µg (Fig. 2) and the blocking of uptake by cold f/F makes precipitation unlikely. If precipitation, or further polymerization were occurring, increasing amounts of cell radioactivity would result from increasing the f/F concentration. In fact an increasing percentage of cell-bound f would be expected, and the opposite occurred.

The high uptake of ¹²⁵I-f by PMNs is not clearly explicable. Cellular metabolism may have been incompletely inhibited, however, as with the macrophages, virtually all the cell-bound ¹²⁵I-f could be removed by subsequent plasmin or trypsin treatment. PMNs have been previously shown to have a great capacity to phagocytize and lyse particulate f. Lewis et al. (18) demonstrated 200–320 × 10⁶ cells could lyse 6 mg particulate f in 3 h. This area requires further investigation.

The nature of the binding site on the macrophage is unknown. The possibilities existed of previously absorbed or synthesized F, f, or CIG binding the ¹²⁵I-f and ¹²⁵I-f/F. CIG is a recently described plasma protein (19) which can be cross-linked to f (20) and is thought to be identical to fibroblast surface antigen (21).
The likelihood of cellular $F$ or $f$ binding the $^{125}\text{I}}$-$f$ was essentially eliminated by continued binding after pretreatment with trypsin or plasmin. CIG is also susceptible to trypsin and plasmin (M. W. Mosesson, personal communication). Additionally, in the experiment comparing macrophages, lymphocytes, and fibroblasts (Table VI), the macrophages bound $f$ at $37^\circ\text{C}$. CIG has been reported not to bind $f$ at $37^\circ\text{C}$ (21). Although not excluded, it is unlikely that other adherent proteins, or residual $F$ or CIG fragments, might bind $f$, but rather some type of membrane receptor is involved. The rapid uptake of $f$ and $f/F$ is similar to that noted for IgG and complement. The quantitative relation between number of $f$ molecules bound and the number of binding sites per cell is uncertain because the protein is not monomeric. In the conditions employed, both $f$ and $f/F$ exist as macromolecular complexes, of an unknown mean number of molecules. Therefore the number of binding sites per cell is less than $6.92 \times 10^6$, as each site binds a polymer containing several $f$ molecules. The number of molecules bound is comparable to the results reported for IgG-binding sites of $0.4-2.5 \times 10^6$ per cell (22-25).

Relatively little $F$, late $F$ degradation products, and late $f$ degradation products were bound as compared to $f$, implying a specificity of uptake that is unique to relatively intact $f$. The observed uptake of $^{125}\text{I}}$-$F$ in $f/F$ complexes was expected based on our previous data (7) indicating the complex is stable in a soluble state. Early $f$ degradation products have also been noted to form large complexes (6). Colvin and Dvorak (26) described macrophage uptake of homologous $F$ using immunofluorescence to detect the protein. It was also surmised that some of the material was $f$ because of a net-like pattern which was absent in warfarin-treated animals. Direct evidence for $f$ binding was not obtained. As in the present results, Ca$^{++}$ was necessary for binding. Our results suggest that $f$ binding may be by a different mechanism than $F$ in that preincubation with $F$ did not block $^{125}\text{I}}$-$f$ uptake, whereas preincubation with $f$ did. The binding of $F$ in the study of Colvin and Dvorak and in the present results may be secondary to several phenomena. It is very difficult to avoid slight denaturation of $F$ during purification and radiolabeling (27). This denatured fraction is rapidly cleared from the blood after injection (28), presumably in the liver and spleen. Part of the small amount of $F$ bound could represent denatured material. Conversely Colvin and Dvorak's positive results with direct staining of cells without prior incubation in plasma would suggest that nonartifactual binding does occur, at least in part. They have hypothesized that $F$ is important in macrophage adherence. The quantitatively greater amounts of $f$ binding found here and the evidence for ingestion noted here (Fig. 4), and by Chang and Boxer (29), indicate a different role for $f$ binding.

Soluble $f$ binding would appear to be the initial step in blood $f$ clearance before ingestion and intracellular catabolism. The very limited reversibility of $f$ binding would be in keeping with this function. It would appear that via this mechanism, the reticuloendothelial system is capable of preventing thrombus formation before formation of microparticulate $f$. The quantitative differences in binding of $F$, $f$, $F$ degradation products, and $f$ degradation products, suggest a fine biochemical discrimination on the cell surface, in keeping with such a homeostatic role.
Guinea pig peritoneal macrophages were demonstrated to bind selectively soluble $^{125}$I-fibrin and fibrin/fibrinogen complexes as compared with fibrinogen, fibrinogen degradation products, and fibrin degradation products. Cellular uptake was considered to be surface receptor binding on the basis of removal of bound $^{125}$I-fibrin by trypsin and because uptake occurred in the presence of metabolic inhibitors. $^{125}$I-fibrin uptake could be blocked by nonradioactive fibrin but not by IgG or immune complexes. Binding was unaffected by prior treatment with plasmin or trypsin but was calcium dependent. Only limited reversibility of binding could be demonstrated after prolonged incubation. Scatchard plots permitted an estimate of the number of bound molecules. At saturation $6.92 \times 10^6$ $^{125}$I-fibrin molecules were bound per cell. Similar binding of fibrin was noted in polymorphonuclear leukocytes, but not lymphocytes or fibroblasts. Soluble fibrin binding may be a host defense mechanism whereby the reticuloendothelial system can remove fibrin from the blood before the development of microthrombi.

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References
1. Lee, L. 1962. Reticuloendothelial clearance of circulating fibrin in the pathogenesis of the generalized Shwartzman reaction. J. Exp. Med. 115:1065.
2. Lee, L., and R. T. McCluskey. 1962. Immunohistochemical demonstration of the reticuloendothelial clearance of circulating fibrin aggregates. J. Exp. Med. 116:611.
3. Shainoff, J. R., and I. H. Page. 1960. Cofibrins and fibrin intermediates as indicators of thrombin activity in vivo. Circ. Res. 8:1013.
4. Jakobsen, E., B. Ly, and P. Kierulf. 1974. Incorporation of fibrinogen with soluble fibrin complexes. Thromb. Res. 4:499.
5. Bang, N. U., and M. L. Chang. 1974. Soluble fibrin complexes. Sem. Thromb. Hemostasis. 1:91.
6. Hansen, M. S., N. U. Bang, R. C. Barton, and L. E. Mattler. 1975. Enhancement of blood coagulation by soluble fibrin complexes. J. Exp. Med. 141:944.
7. Sherman, L. A., S. Harwig, and J. Lee. 1975. In vitro formation and in vivo clearance of fibrinogen:fibrin complexes. J. Lab. Clin. Med. 86:100.
8. Hayne, O. A., and L. A. Sherman. 1973. In vivo behavior of fibrinogen fragment D in experimental renal, hepatic, and reticuloendothelial dysfunction. Am. J. Pathol. 71:219.
9. Fletcher, A. P., N. Alkaersig, J. R. O'Brien, and V. G. Tulevski. 1970. Blood hypercoagulability and thrombosis. Trans. Assoc. Amer. Physicians 83:159.
10. Niewiarowski, W., and V. Gurewich. 1971. Laboratory identification of intravascular coagulation: the SDPS test for the detection of fibrin monomer and fibrin degradation products. J. Lab. Clin. Med. 72:685.
11. Graeff, H., R. von Hugo, and R. Hafter. 1973. In vivo formation of soluble fibrin monomer complexes in human plasma. Thromb. Res. 3:465.
12. Bachmann, P., and O. Pichairut. 1971. Hypercoagulability syndrome in patients with renal disease. Fed. Proc. 30:424. (Abstr.)
13. Blomback, B., and M. Blomback. 1956. Purification of human and bovine fibrinogen. *Arkiv Kemi.* 10:415.
14. McFarlane, A. S. 1963. In vivo behavior of $^{131}$I-fibrinogen. *J. Clin. Invest.* 42:346.
15. Greineder, D. K., and A. S. Rosenthal. 1975. Macrophage activation of allogenic lymphocyte proliferation in the guinea pig mixed leukocyte culture. *J. Immunol.* 114:1541.
16. Kulczycki, A., Jr., T. A. McNearney, and C. W. Parker. 1976. The basophilic leukemia cell receptor for IgE. I. Characterization as a glycoprotein. *J. Immunol.* In press.
17. Deutsch, D. G., and E. T. Mertz. 1970. Plasminogen: purification from human plasma by affinity chromatography. *Science (Wash. D. C.)*. 170:1095.
18. Lewis, J. H., I. L. Szeto, W. L. Bayer, and D. C. Curiel. 1972. Leukofibrinolysis. *Blood.* 40:844.
19. Mosesson, M. W., and R. A. Umfleet. 1970. The cold insoluble globulin of human plasma. *J. Biol. Chem.* 245:5728.
20. Mosher, D. F. 1975. Cross-linking of cold-insoluble globulin by fibrin-stabilizing factor. *J. Biol. Chem.* 250:6614.
21. Ruoslahti, E., and A. Vaheri. 1975. Interaction of soluble fibroblast surface antigen with fibrinogen and fibrin. *J. Exp. Med.* 141:497.
22. Phillips-Quagliata, J. M., B. B. Levine, F. Quagliata, and J. W. Uhr. 1971. Mechanisms underlying binding of immune complexes to macrophages. *J. Exp. Med.* 133:589.
23. Arend, W. P., and M. Mannik. 1973. The macrophage receptor for IgG: number and affinity of binding sites. *J. Immunol.* 110:1455.
24. Leslie, R. G. Q., and S. Cohen. 1974. Cytophilic activity of IgG2 from sera of unimmunized guinea pigs. *Immunology.* 27:577.
25. Unkeless, J. C., and H. N. Eisen. 1975. Binding of monomeric immunoglobulins to Fc receptors of mouse macrophages. *J. Exp. Med.* 142:1520.
26. Colvin, R. B., and H. F. Dvorak. 1975. Fibrinogen/fibrin on the surface of macrophages: detection, distribution, binding requirements, and possible role in macrophage adherence phenomena. *J. Exp. Med.* 142:1377.
27. McFarlane, A. S. 1970. Synthesis and degradation of plasma proteins. In Plasma Protein Metabolism. M. A. Rothschild and T. Waldmann, editors. Academic Press, Inc., New York. 51.
28. Metzger, J., R. Seeker-Walker, K. Krohn, M. Welch, and E. J. Potchen. 1973. Unsatisfactory biological behavior of $^{1}$-fibrinogen labelled by the chloramine-T method. *J. Lab. Clin. Med.* 82:267.
29. Chang, M. L., and L. A. Boxer. 1976. Cellular clearance of fibrinogen-fibrin degradation products. *Fed. Proc.* 35:648. (Abstr.)