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Part B: Monitoring and Treatment of Shock

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Contents

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Contents of Part A: Pathophysiological Role of Mediators and Mediator Inhibitors in Shock

1. THE PATHOPHYSIOLOGICAL ROLE OF MEDIATORS AND INHIBITORS THEREOF IN SHOCK

1.1. Complement—Granulocytes

1.2. Proteases

First Vienna Shock Forum, Part B: Monitoring and Treatment of Shock, pages 41–49

Quantification of Granulocyte Enzymes/Proteins with Immunoassays

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This presentation provides the analytical background for the data of many experimental and clinical studies presented during the symposium, which are concerned with the role of neutrophil activation in the pathogenesis of shock. Figure 1 shows in a schematic way the events leading to, and produced by the activation of neutrophils. The proteolytic and oxidative action of neutrophil products, when released in excess of the local inhibitor concentrations, is one of the pathogenetic mechanisms in development of organ failure ultimately leading to shock.

We have developed immunoassays for 3 lysosomal proteins from the neutrophil;

- Elastase from the azurophilic granules, a neutral proteinase of very broad substrate specificity,

- Myeloperoxidase, also from the azurophilic granules, an enzyme involved in the oxidative activity of the neutrophil,

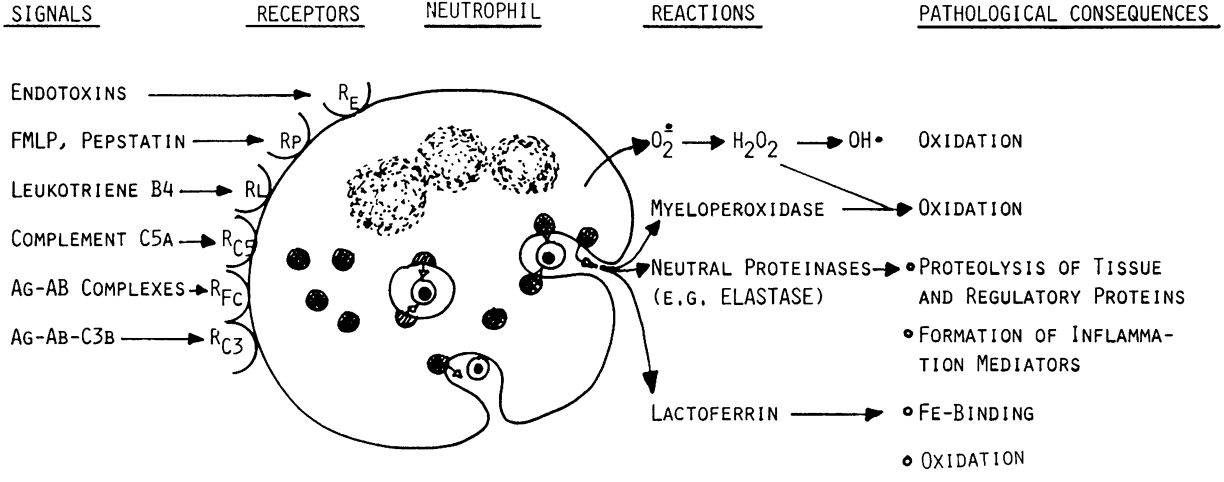


Figure 1

The Biochemistry of Neutrophil Activation

- Lactoferrin from the specific granules, an iron-binding protein, also involved in the oxidative mechanisms.

The assay principle of the tests is summarized in Figure 2. All assays are double antibody, solid phase, enzyme immuno assays. The marker enzyme is alkaline phosphatase. A special case is the elastase assay. PMN-elastase occurs in the blood in form of it's complex with alpha$_1$-proteinase inhibitor. The analyte measured, therefore, is the elastase-alpha$_1$-proteinase-inhibitor complex. The first antibody is directed against the enzyme, the second antibody against the inhibitor.

Not all of the elastase is bound to alpha$_1$-proteinase inhibitor. As shown in Figure 3, in human blood about 90 % of elastase is bound to alpha$_1$-proteinase inhibitor, and about 10 % to alpha$_2$-macroglobulin. The elastase-alpha$_2$-macroglobulin complex has a half life of only 10 minutes, whereas the elastase-alpha$_1$-proteinase-inhibitor complex has a half life of about 1 hour. The analytical error inflicted by measuring only the fraction of elastase bound to alpha$_1$-proteinase inhibitor, is negligible, therefore.

Details of the assay procedures for elastase-complex, myeloperoxidase, and lactoferrin are summarized in Table 1. The assay characteristics are given in Table 2, including the concentration of these proteins in the plasma of healthy human subjects (reference range).

The assays described are in the process of extensive evaluation of their usefulness as biochemical "Shock Predictors".

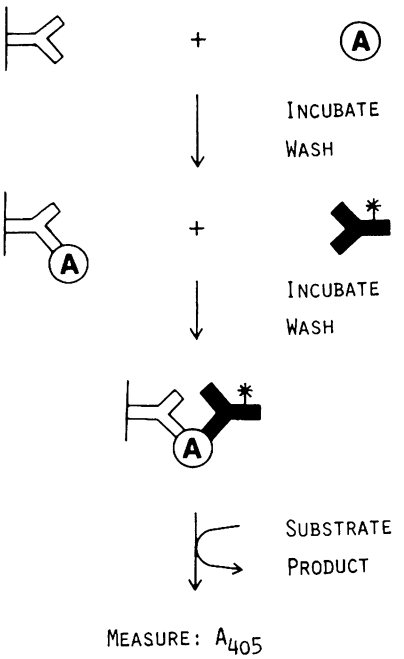
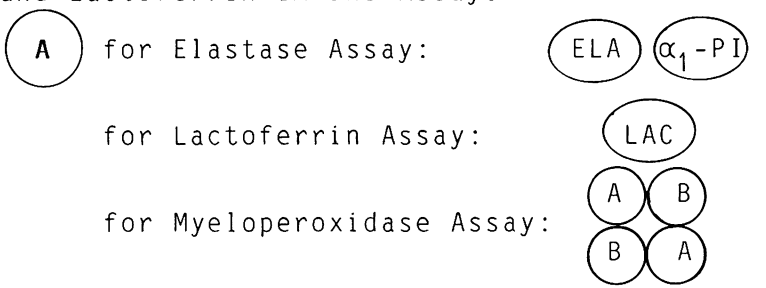


Figure 2

Assay Principle for Elastase, Myeloperoxidase, and Lactoferrin Immuno Assays



* Alkaline Phosphatase

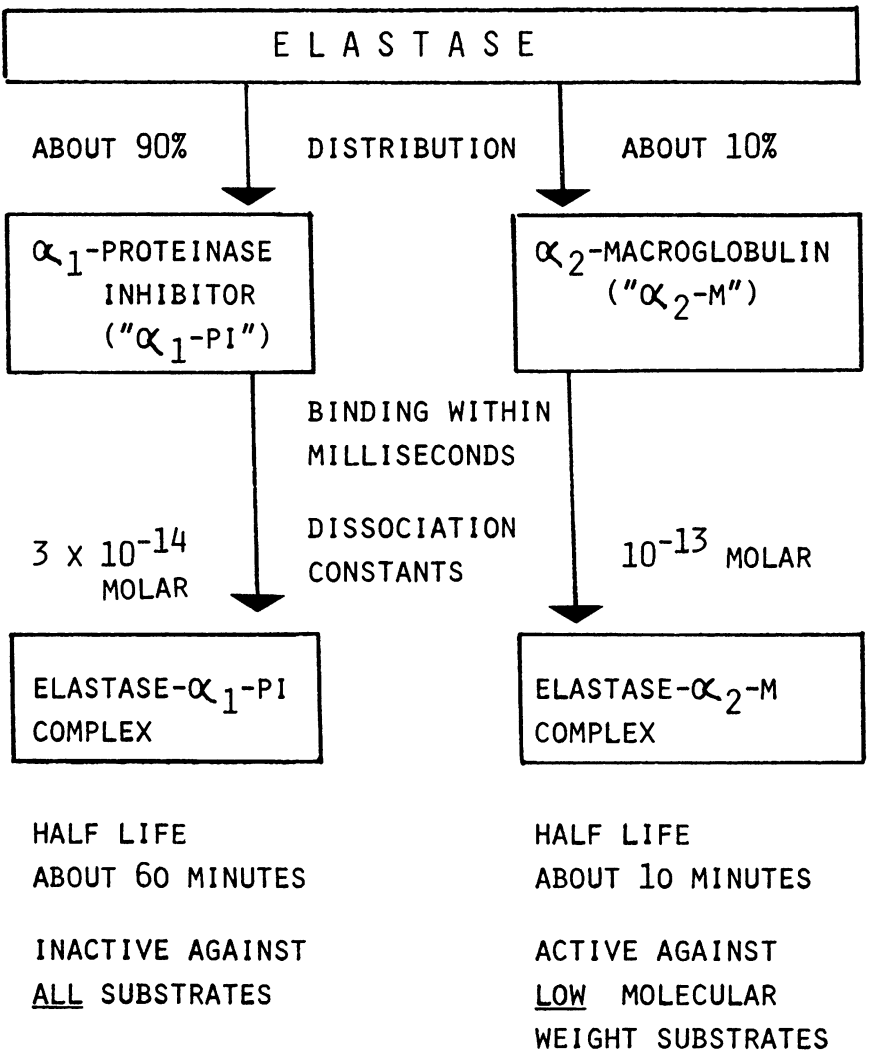


Figure 3

PMN Elastase and Inhibitor Systems in Blood

TABLE 1. ASSAY PROCEDURE

	ELASTASE COMPLEX	MYELOPEROXIDASE	LACTOFERRIN
ASSAY TYPE	TWO-SITE ELISA	ELISA	ELISA
SOLID-PHASE ANTIBODY	A-ELASTASE	A-MYELOPEROXIDASE	A-LACTOFERRIN
SAMPLE DILUTION	1:51	1:21	1:50
INCUBATION TIME 1 (HR)	1	1	2
WASHING STEPS	3	3	3
CONJUGATE	A-α_1-PI-AP	A-MPO-AP	A-LAC-AP
INCUBATION TIME 2 (HR)	1	2	2
WASHING STEPS	2	2	3
SUBSTRATE	---- P-NITROPHENYL PHOSPHATE ----------		
INCUBATION TIME 3 (HR)	1.5	1	1
REACTION VOLUME (ML)	0.5	0.5	0.5
INCUBATION TEMPERATURE	RT	RT	RT

ABBREVIATIONS: ELISA = ENZYME LINKED IMMUNOSORBENT ASSAY
α_1-PI = α_1-PROTEINASE INHIBITOR (EX "α_1-ANTI TRYPSIN")
MPO = MYELOPEROXIDASE
LAC = LACTOFERRIN
AP = ALKALINE PHOSPHATASE

TABLE 2. ASSAY CHARACTERISTICS

	ELASTASE COMPLEX	MYELOPEROXIDASE	LACTOFERRIN
STANDARD CURVE	0 - 10 µG/L	0 - 20 µG/L	0 - 10 µG/L
CALIBRATION CURVE: CALCULATION	LINEAR REGRESSION	LINEAR REGRESSION	LINEAR REGRESSION
DETECTION LIMIT (BLANK + 3 SD)	0,25 µG/L	0,25 µG/L	0,25 µG/L
SAMPLES:			
SERUM	Ø	Ø	+
EDTA PLASMA	+	+	+
CITRATE PLASMA	+	+	+
IMPRECISION:			
WITHIN-RUN (%)	4 - 8 (N=10)	7 - 9 (N=15)	2 - 5 (N=10)
BETWEEN-RUN(%)	3 - 8 (N=10)	5 -12 (N= 9)	4 -10 (N=10)
REFERENCE RANGE (MEAN ± S.D.) IN CITRATE PLASMA	67 ± 29 µG/L	36 ± 12 µG/L	137 ± 51 µG/L

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