SECONDARY AMYLOIDOSIS: FROM AN ABSTRUSE PATHOLOGIC CURIOSITY TO A TREATABLE MOLECULAR DISEASE

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For over 100 years, secondary amyloidosis has remained largely an abstruse curiosity of pathologists. It is traditionally viewed as an untreatable progressive disease that results from chronic infections or inflammatory diseases. During the past 5 years, this view has been dramatically changed, owing to a series of remarkable observations concerning the chemistry and metabolism of amyloid. The disease can now be precisely defined in modern biochemical terms. If Rokitansky and Virchow, the two pathologists who initially described the pathologic condition of amyloidoisis over 100 years ago, were alive today, it would come as a great surprise to them to find that tissue amyloid originates from a normal plasma protein that fluctuates a 1000-fold within hours of an acute inflammatory stimulus. In this Grand Round, I will review current concepts of the pathogenesis of secondary amyloidosis, emphasizing how detailed knowledge of the biochemistry of amyloid is leading to the development of rational therapeutic approaches.

CASE REPORT - 25 year old Iranian male

- Age 5 –episodic attacks of abdominal pain and fever; attack every 1 to 2 months
- Age 20 –student at Univ. of Texas at Austin; diagnosis of FMF; negative family history (3 sibs at risk)
- Age 21 –attack of pleuritis
- Age 22 –proteinuria; amyloidosis confirmed by rectal biopsy
- Age 23 –nephrotic syndrome with anasarca; serum albumin, 1.6 gm %; edema disappeared after 2 weeks of Lasix; diuretics discontinued
- Age 24 –hypotension; "low" plasma cortisol and "high" plasma ACTH; ? adrenal insufficiency; treated with hydrocortisone and fluorohydrocortisone; serum creatinine, 6 mg %
- Age 25 –admitted to PMH in June 1983; BP 80/50; no edema; BUN, 77 mg %; urine protein, 20 g/day; creatinine clearance, 6.6 ml/min; ACTH stimulation test (50 units/24 hr IV) → plasma cortisol rose from 1 μg% to 9 μg%; treated with hydrocortisone, fluorohydrocortisone, colchicine, and peritoneal dialysis.

I. CLINICAL ASPECTS OF SECONDARY AMYLOIDOSIS

Fig. 1.

AMYLOIDOSIS - HISTORICAL LANDMARKS

• 1842	Rokitansky	Chronic sepsis
• 1858	Virchow	Speculations on chemical nature
• 1859	Kekule and Friedreich	Protein, not starch
• 1903	Ehrlich	Staining characteristics
• 1923	Kuczynski	Mouse model — casein
• 1924	Domagk	Reticuloendothelial system
• 1970's	Glenner Benditt Franklin	Biochemistry and cell biology

Fig. 2.

CLASSIFICATION OF AMYLOIDOSIS

CLINICAL DESIGNATION	TYPE	PROTEIN CONSTITUENT OF TISSUE AMYLOID
Primary		
• Plasma Cell Dyscrasias	AL	Fragments of immunoglobulin light chains
Secondary		
• Chronic Inflammatory Diseases • FMF	AA	Acute phase reactant
Heredofamilial		
• Portugese variety	AF	Prealbumin
Localized		
• Medullary Thyroid Carcinoma	AE_1	Thyrocalcitonin
• Diabetes Mellitus	AE_2	Glucagon, ? insulin
Senile Amyoloid		
• Heart	AS	Prealbumin
• Brain	AS	Prealbumin

Fig. 3.

ETIOLOGY OF SECONDARY AMYLOIDOSIS

- Genetic — Familial Mediterranean Fever
- Nongenetic — Osteomyelitis - paraplegics
  Tuberculosis
  Bronchiectasis
  Rheumatoid Arthritis and Spondylitis
  Hodgkin's Disease
  Chronic Inflammatory Bowel Disease
  Renal Cell Carcinoma
  Drug Addicts

Fig. 4.

FAMILIAL MEDITERRANEAN FEVER

- Autosomal Recessive Disorder
- Mediterranean Geographic Distribution – Arabs, Turks, Sephardic Jews > Ashkenazic Jews, Armenians, Italians, Greeks
- Periodic Attacks That Revert Spontaneously – Peritonitis, Pleuritis, Arthritis
- Erysipeloid-like Erythema
- Prevention by Long-term Administration of Colchicine

II. STRUCTURAL ASPECTS OF AMYLOID PROTEIN

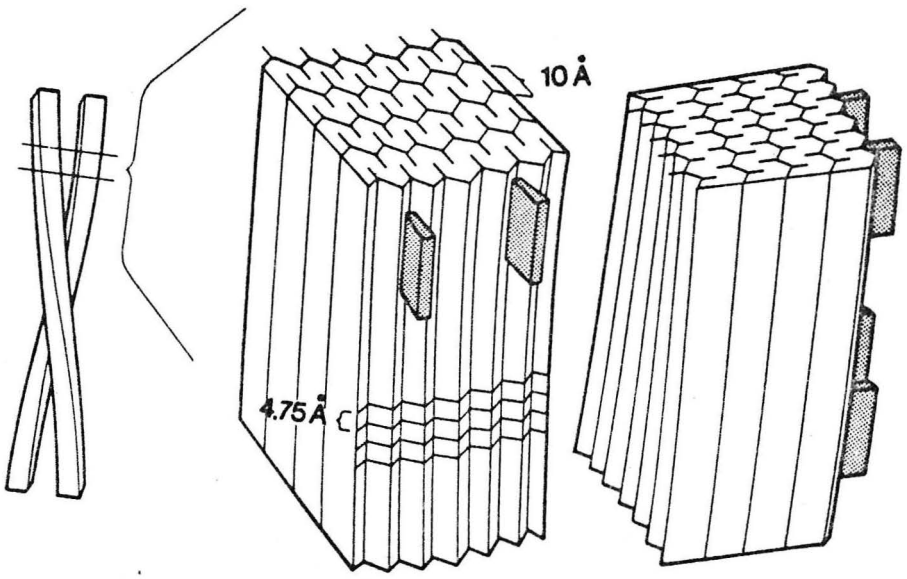


Fig. 5. Twisted β-pleated sheet configuration of amyloid protein demonstrating the sites of binding of Congo red dye.

Fig. 6.

AMYLOID PROTEINS

AA	Amyloid A Fibril	Tissues
SAA	Serum Amyloid A (Acute Phase Reactant)	Plasma

Fig. 7.

STRUCTURAL RELATION BETWEEN SAA AND AA

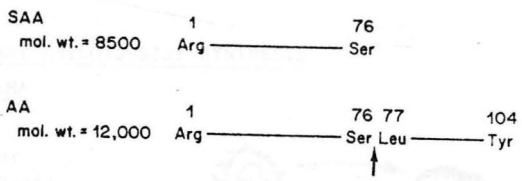


Fig. 8. Polyacrylamide gel electrophoresis of SAA and AA proteins.

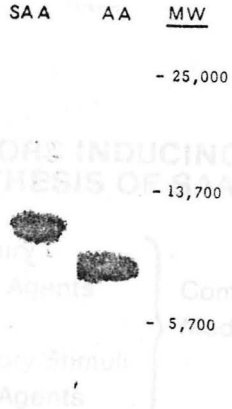
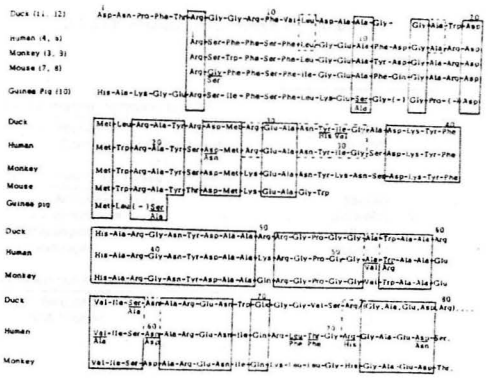


Fig. 9. Amino acid sequence of AA proteins from multiple species.



III. PATHOGENESIS OF SECONDARY AMYLOIDOSIS: SYNTHESIS AND SECRETION INTO PLASMA

Fig. 10. Model for pathogenesis of secondary amyloidosis.

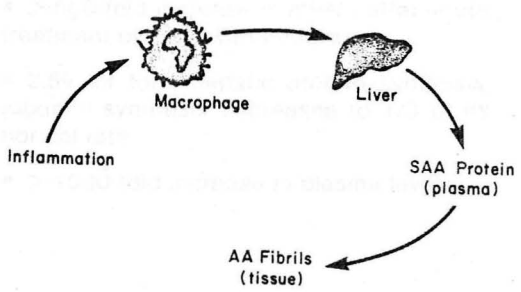


Fig. 11

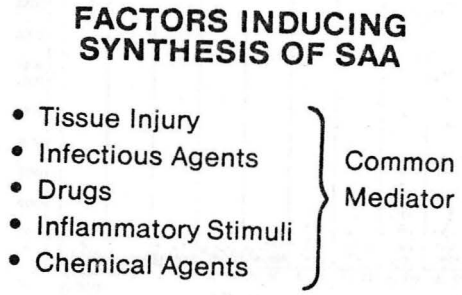


Fig. 12.

ACUTE PHASE PROTEINS IN HUMANS

	NORMAL PLASMA CONCENTRATION (mg %)
Concentration Increases by 50%	
Ceruloplasmin	15-60
C3 - Complement Component	80-170
Concentration Increases 2 to 3-fold	
α_1-Acid Glycoprotein	55-140
α_1-Antitrypsin	200-400
Haptoglobin	40-180
Fibrinogen	200-450
Concentration Increases up to 1000-fold	
C-Reactive Protein	< 0.5
SAA Protein	<10

Fig. 13.

SYNTHESIS OF SAA

- Liver
- > 500-fold increase in mRNA after acute treatment of mice with endotoxin
- 2.5% of total hepatic protein synthesis Albumin synthesis decreases to 1/3 of its normal rate
- > 1000-fold increase in plasma level

Fig. 14.
Concentration of SAA in normal subjects in relation to age.

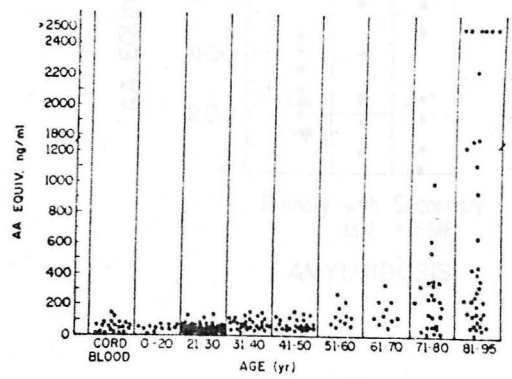


Fig. 15. Concentration of SAA in various disease states.

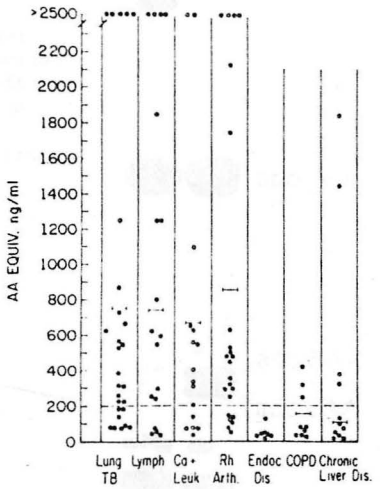
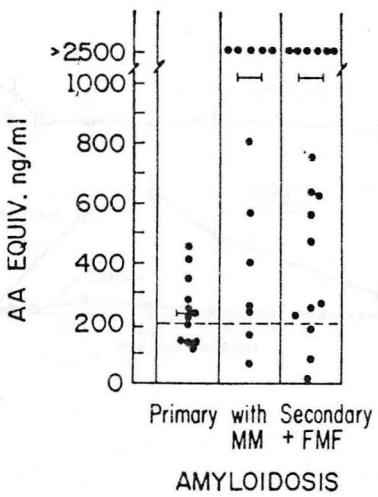


Fig. 16. Concentration of SAA in amyloidosis.



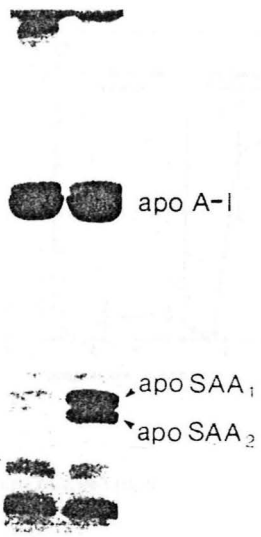


Fig. 17. SDS polyacrylamide gel electrophoresis of normal mouse plasma HDL (left lane) and mouse plasma HDL 20 hours after endotoxin administration (right lane).

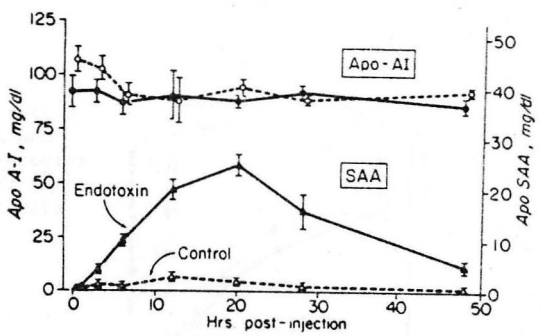


Fig. 18. Induction of SAA by endotoxin in mice.

Fig. 19. Appearance of SAA in HeJ mice treated with lipopolysaccharide (A), normal serum from HeN mice (B), or with serum from lipopolysaccharide-treated HeN mice.

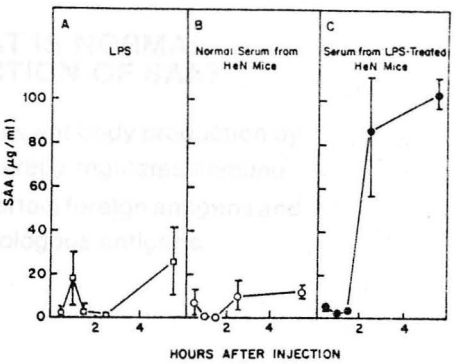


Fig. 20.

INTERLEUKIN-I (IL-I)

1. Protein with mol wt = 15,000
2. Synthesized by macrophages undergoing an immune response
3. Actions
   - Activates B and T cells
   - Raises body temperature
   - Increases number of circulating neutrophils
   - Induces hepatic synthesis of acute phase reactants, such as SAA

Fig. 21. Synthesis and secretion of apo A-I of HDL and SAA by mouse hepatocytes before (●---●) and after (O——O) treatment with endotoxin.

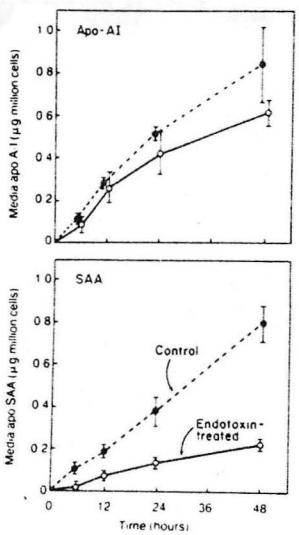


Fig. 22

WHAT IS NORMAL FUNCTION OF SAA?

SAA suppresses antibody production by B cells and thereby regulates immune response to certain foreign antigens and to altered autologous antigens.

IV. PATHOGENESIS OF SECONDARY AMYLOIDOSIS: DEGRADATION AND TISSUE DEPOSITION

Fig. 23. Degradation of SAA and AA by human blood monocytes.

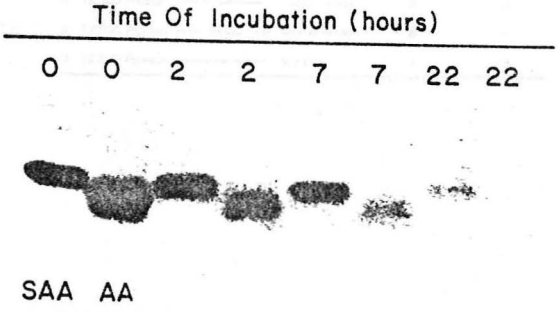


Fig. 24. Patterns of degradation of SAA by human monocytes.

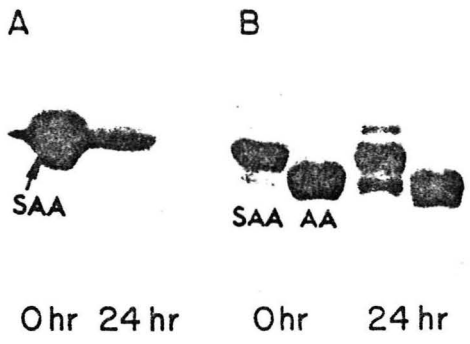


Fig. 25. Patterns of degradation of SAA by human monocytes from normal subjects and from patients with secondary amyloidosis.

DEGRADATION OF SAA

PATHWAY OF DEGRADATION	NUMBER OF SUBJECTS	
	NORMAL	2° AMYLOID
1. 12,500 Protein → Amino Acids	8	0
2. 12,500 Protein → 8,000 → Amino Acids	8	4
3. 12,500 Protein → 8,000	4	0

Fig. 26.

AMYLOID ENHANCING FACTOR

- Glycoprotein extracted from reticulo-endothelial cells of spleen or liver of mice that have been subjected to repeated episodes of inflammation
- Action - Accelerates extracellular deposition of AA fibrils in mice with elevated plasma levels of SAA

Fig. 27. Kinetics of amyloid deposition in spleen of mice treated with (●---●) and without (O——O) amyloid enhancing factor.

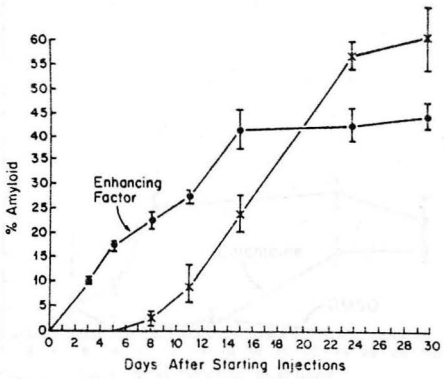


Fig. 28.

GENETICS OF AMYLOID DEPOSITION

Strain of Mice	Number Tested	Number Resistant to Amyloid Deposition
CBA/J	20	0
A/J	20	20
F_1 (CBA/J x A/J)	20	0
F_1 x A/J	43	19

V. TREATMENT OF SECONDARY AMYLOIDOSIS

Fig. 29. Effect of colchicine in 62 patients with Familial Mediterranean Fever.

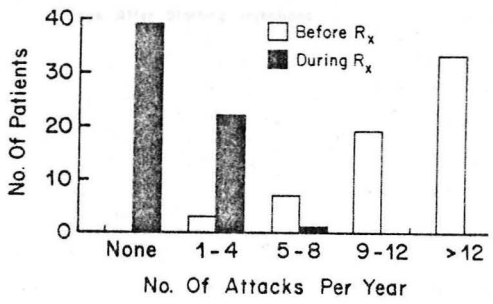


Fig. 30. Effect of colchicine and DMSO on kinetics of amyloid deposition in liver of caesin-treated mice.

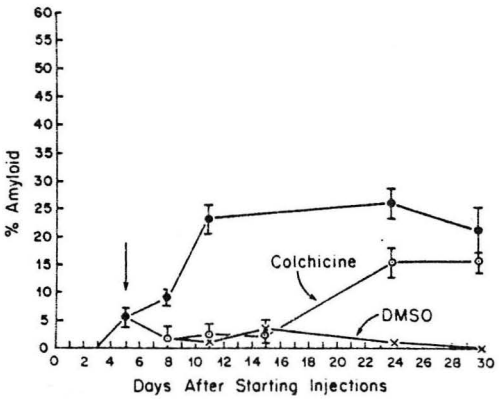
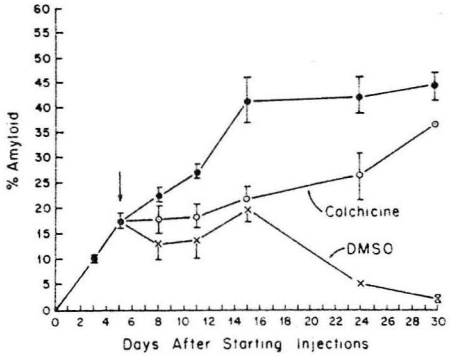


Fig. 31. Effect of colchicine and DMSO on kinetics of amyloid deposition in spleen of caesin-treated mice.



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