ESSAY ON ALPHA-ANTITRYPSIN DEFICIENCY IN INFANCY AND CHILDHOOD

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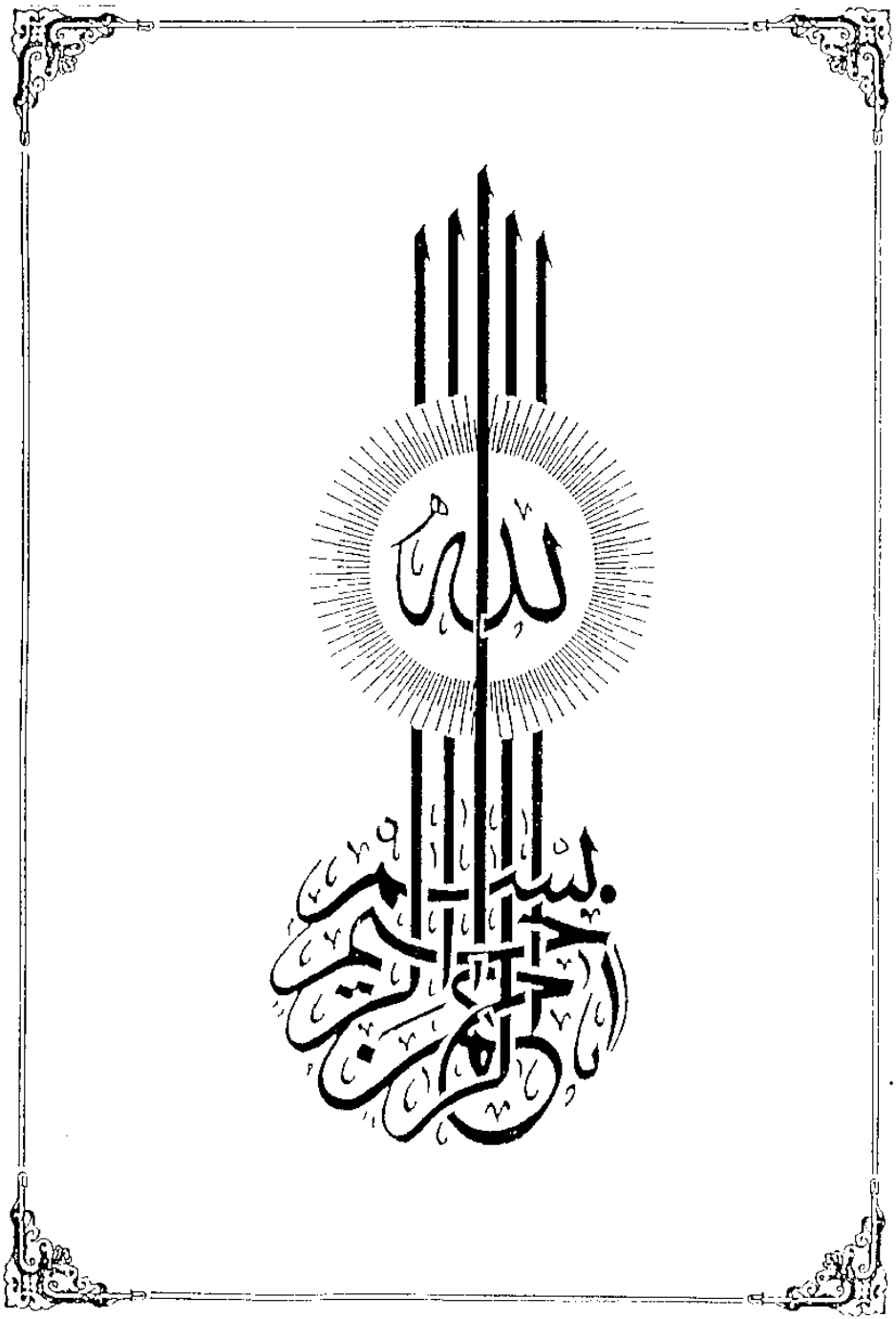

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ABBREVIATIONS

α_1AT	=	Alpha$_1$-antitrypsin.
BAL	=	Bronchoalveolar lavage.
BPD	=	Bronchopulmonary dysplasia.
cDNA	=	Complementary deoxyribonucleic acid.
CRNS	=	Corticosteroid responsive nephrotic syndrome.
DNA	=	Deoxyribonucleic acid.
MPGN	=	Membranoproliferative glomerulonephritis.
mRNA	=	Messenger ribonucleic acid.
OLT	=	Orthotopic liver transplantation
PAS	=	Periodic acid schif.
Pi*	=	Protease inhibitor.
PKU	=	Phenylketonuria.
RDS	=	Respiratory distress syndrome.
RFLP	=	Restriction fragment length polymorphism.
SGOT	=	Serum glutamic oxaloacetate transaminase.
SGPT	=	Serum glutamic pyruvate transaminase.
TIC	=	Trypsin inhibitory capacity.

N.B.*: It was agreed that normal homozygous gene for protease inhibitor will be called PiMM (or PiM) and the deficiency homozygous genes will be designated PiZZ (PiZ), PiSS(PiS), Pi null, Pi mudurate. The heterozyous conditions will be written as PiMZ, PiSZ, PiS-. Allelic symbols for protease inhibitor will be written as Pi^M, Pi^{MZ}, Pi^S, Pi^Z (Cox et al., 1980).

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INTRODUCTION

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An alpha$_1$-glycoprotein was isolated by Schultz et al. (1955) and was given the name alpha$_1$-antitrypsin (α_1AT) after its capacity to link trypsin had been observed (Schultz, 1962).

It represents 90% of the alpha$_1$-globulin fraction in human serum protein electrophoresis (Heimburger et al., 1964).

α_1AT exhibits considerable electrophoretic and genetic polymorphism (Fagerhol and Geddle-Dahl, 1969). This polymorphic system has been designated the Pi (protease inhibitor) system (Fagerhol, 1968). More than 40 genetic variants of α_1AT were reported up to 1982 (Carrell et al., 1982).

Individuals with α_1AT deficiency have a different type of α_1AT, with a different electrophoretic mobility from the normal. The deficient type is named Pi type Z (genotype ZZ), the normal is Pi type M (genotype MM) (Fagerhol,1968).

Of particular interest are the alleles that lead to lower than normal concentration of serum α_1AT, namely PiZ, PiS and Pinull.

Laurell and Eriksson (1963) described the association between pulmonary emphysema and severe genetic deficiency of α_1AT. Further interest in this disorder was stimulated by studies of Sharp and his Colleagues (1969), who reported an association between α_1AT deficiency and liver cirrhosis in infants and children. The liver disease in infancy frequently presents as "neonatal hepatitis syndrome" with prolonged jaundice, failure to thrive, hepatomegaly and sometimes, splenomegaly (Moroz et al., 1976 & Cutz and Cox, 1979).

Since the heterozygate state (PiMZ) exists in up to 3% of the population and the homozygote state (PiZZ) in up to 0.07% (1 in 1,500), the condition of any infant presenting with direct hyperbilirubinemia and hepatomegaly or even hepatomegaly without jaundice should be evaluated for α_1AT deficiency (Treem, 1987).
Some children, perhaps as many as two thirds, recover from their liver abnormalities and became virtually normal (Moroz, 1976).

Renal involvement was found in children who died of cirrhosis (Moroz et al., 1976 a).

Besides the presence of certain genetic variants, low level of α_1AT have been detected secondary to the respiratory distress syndrome in newborn (Evans et al., 1970; Mathis et al., 1973; Abdel Gawad et al., 1983 and Chiniara et al., 1986), terminal liver failure (Talamo, 1975).

There is no practical method for treating the genetic deficiency of α_1AT at this time. However, a number of different approaches are being considered. These approaches include: stimulation of α_1AT production by the liver (Gadek et al., 1980), use of synthetic elastase inhibitor (Kleinerman et al., 1980), use of purified human α_1AT (Wewers et al., 1987), liver transplant (Hood et al., 1980) and gene therapy (Chytil et al., 1988).

AIM OF ESSAY

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On the bases of the previously mentioned scientific work from all over the world to investigate the role α_1AT deficiency, this essay aims at drawing a full picture of not only the genetic role and clinical disorders associated with α_1AT but also of the prognosis and the possibilities of treatment.

The objectives of this essay are to throw light on the value of α_1AT and the role of its genetic deficiency in infancy and childhood. It's correlation with later occurrence of liver cirrhosis and emphysema, as well as it's value in the diagnosis of the occurrence of hyaline membrane disease in the newborn will also be reviewed.

GENETIC ASPECT
OF
ALPHA$_1$- ANTITRYPSIN DEFICIENCY

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Fagerhol and Braend (1965) developed an acid starch gel system showing genetic variation in the prealbumin region. Later on, Fagerhol and Laurell (1967) found that α_1AT migrates anodally in the prealbumin region in an acid starch medium separating into three major and five minor hands. Thus, the net effect of this system seems to reduce the net charge of albumin to that of α_1AT. Finally, Fagerhol (1968) suggested that the system be called Pi for protease inhibitor. These Pi types have been designated alphabetically according to their mobility in acid starch gel. The most common type is PiM, produced by the Pi^M allele. The variants anodal to M have desingation from B to L, cathodal from N to Z. At least 24 different alleles have been identified at the Pi locus at that time (Fagerhol and Gedde-Dahl, 1969).

Mode of Inheritance

Erikson (1965) mentioned that deficiency of α_1AT was inherited as a simple autosomal recessive trait. In families in which one parent had a low level α_1AT and the other parent had a normal value, all children had an intermediate level. When both parents had intermediate α_1AT concentrations, the children

had low, intermediate and normal values in the classic ratio of 1:2:1. These observations are consistent with interpretation that low values are caused by homozygosity for a "deficiency" gene, intermediate values by heterozygosity, and normal values by homozygosity for the "normal" gene (Kueppers and Black, 1974).

Furthermore, the inheritance of a specific type of α_1AT is said to be codominant because each genetic type is expressed in the heterozyote. For example, the heterozygosity type MZ is an individual who produces both M and Z types α_1AT. However, the incidence of liver or lung disease appears to be recessive, as it occurs only in those with a deficiency (Pi ZZ), while heterozygotes (Pi MZ) are usually normal. The implication of this recessive disease risk is that 1 in 4 sibs of a patient with α_1AT deficiency will also have the deficiency (Cox, 1983).

Genetic Variants

The Pi^M alleles are by far the most common allele in all populations and races, followed by PiS and PiZ. Homozygous PiMM is the most common α_1AT phenotype; present in more than 90% of the general population and produces a "normal" quantity and quality of α_1AT (Bohm, 1980).