Determination Of Serum Alpha$_1$-Antitrypsin And Various Glycoproteins In Liver Cirrhosis In Children.

A Thesis Submitted For The Partial Fulfilment Of Master Degree In Pediatrics.

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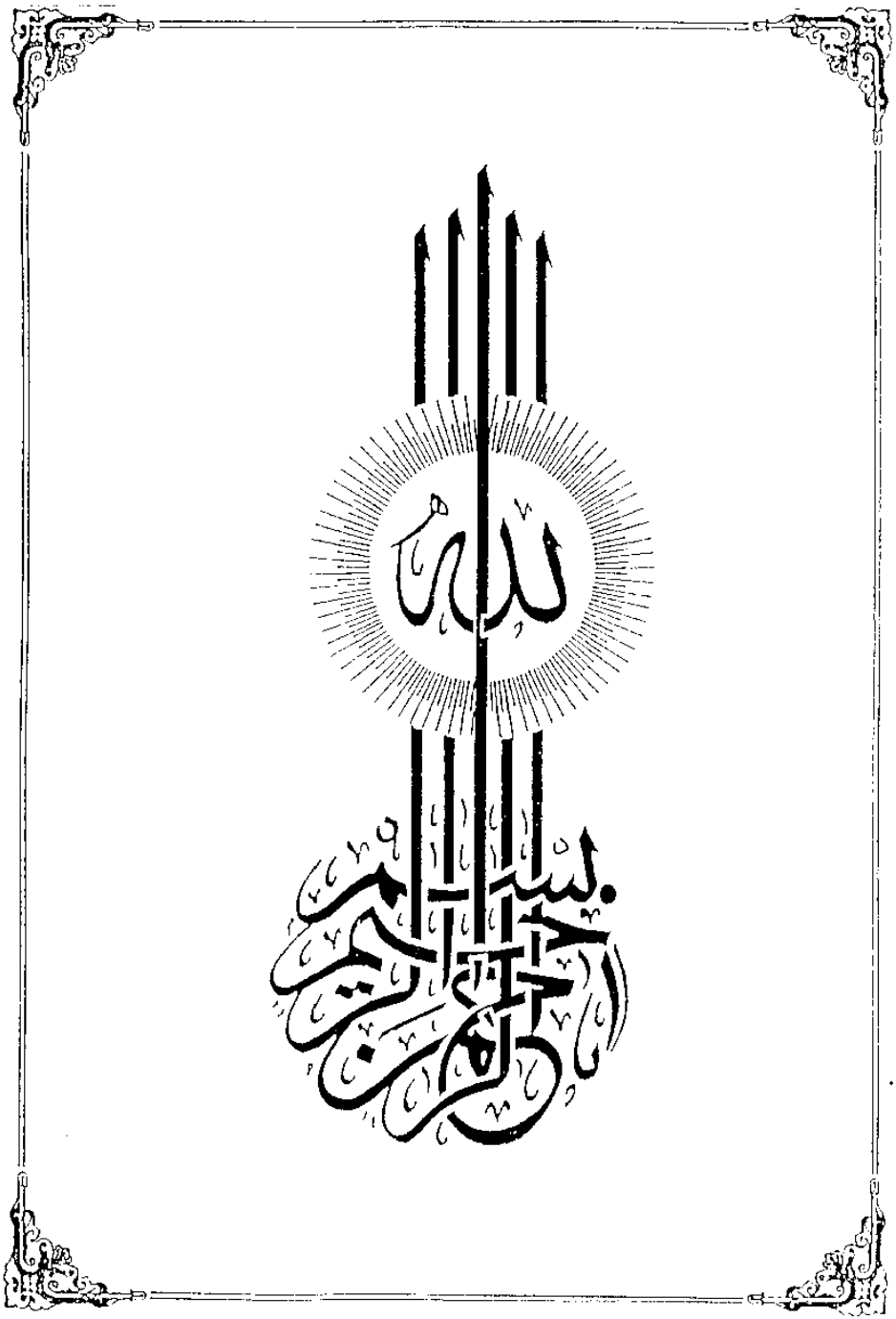

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INTRODUCTION

AND

AIM OF WORK

nall 1980), this work aims to study the serum level of e glycoproteins in cases of liver cirrhosis of various ology in childhood as well as the impact of liver ry on them.

In attempt to uncover causes of cryptogenic liver hosis, many scientists reported an association between α_1-antitrypsin deficiency and cirrhosis in infants children (Kueppers 1967, Talamo 1975, Sharp 1976, hitz 1980, David Hull 1981 and others). Since then, nsive researches are being done to define the role of rited alpha$_1$-antitrypsin deficiency and possible other ciencies of these protective proteins against the ue-damaging effect of both endogenous and exogenous mes, in causation of liver disease.

So, in addition, this work aims to throw light on tic affection that may occur in congenital deficient viduals having subnormal serum levels of alpha$_1$-trypsin and other antienzymatic proteins, e.g.: α_2-Macroglobulin.

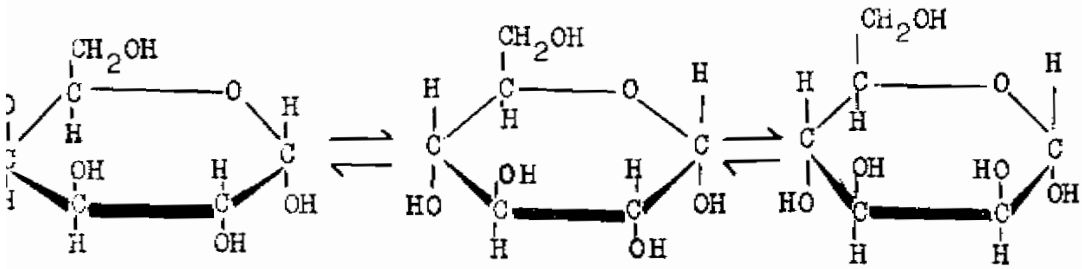
REVIEW OF LITERATURE

in glycoproteins. Fucose (a deoxy galactose), acetyl-glucosamine, and acetyl-galactose amine are the most frequently found hexoses in the glycoproteins, two pentoses, arabinose and xylose, also occur in glyco-proteins. A common constituent of glycoproteins is neuraminic acid.

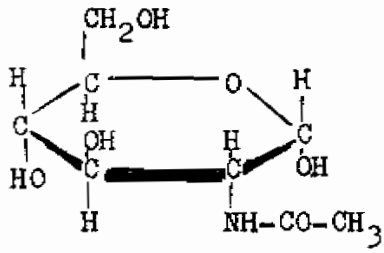
It has become customary to reserve the term glycoprotein for those entities containing less than 4% of amino-sugars (hexose amines) and the term muco-protein is used when this figure is exceeded (Latner 1975).

Fucose and sialic acid always occupy peripheral positions some distance from the polypeptide chain. In contrast acetyl glucose amine and galactose are usually found nearest the protein, often forming a part of the carbohydrate to protein linkage. Only 5 of the 20 naturally occuring amino acids are known to form link-ages with carbohydrates in the glycoproteins. These are asparagine, serine, threonine, hydroxylysine, and hydroxyproline. (Harper et al 1977).

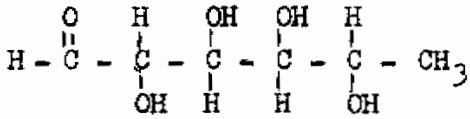
Some of the carbohydrate components of glyco-proteins with their origin and examples of glycosidic linkages between carbohydrate and protein are illust-rated below.



D galactose ∝ D glucose ∝ D mannose



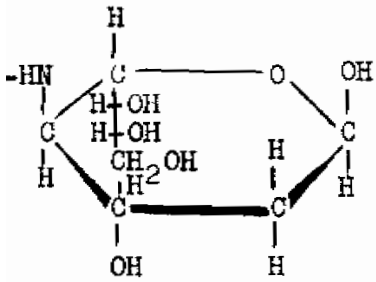
N-acetyl-glucosamine



L-Fucose
(6-dexoy L-galactose)

N-acetyl-glucosamine-6-P $\xrightarrow{\text{Epimerase}}$ N-acetyl-mannosamine-6-P

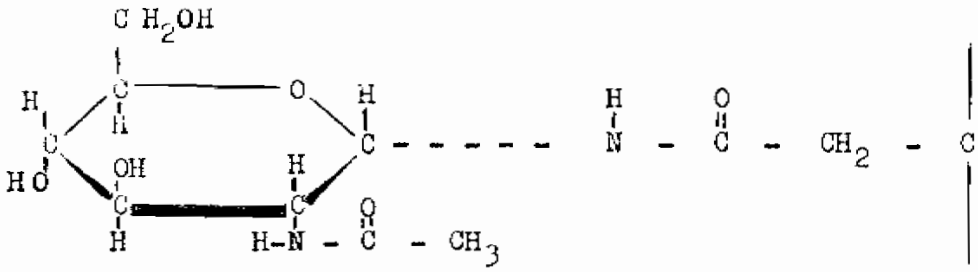
Phosphoenolpyruvate



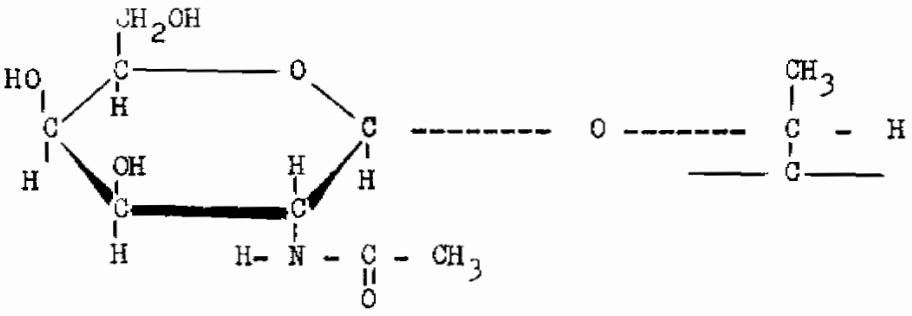
Sialic acid ← N-acetyl-neuraminic acid-9P
(mucopolysaccharide)
or
(glycoprotein)

-acetylneuraminic acid
or sialic acid

of the carbohydrate components of glycoproteins(Harper et al,1977



Linkage of N-acetylglucosamine and asparagine.



Linkage of N-acetylgalactosamine and threonine

Examples of glycosidic linkages between carbohydrates and proteins (Harper et al, 1977).

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Classification of glycoproteins:

Glycoproteins may be: α_1-globulins (α_1-antitrypsin, α_1-easily precipitable glycoprotein, transcortin. 4.65 postalbumin, tryptophan poor-α_1-glycoprotein), α_2-globulins (haptoglobins, ceruloplasmin, α_2-macroglobulin, α_2 HS glycoprotein, Zn α_2-glycoprotein), B-globulins (transferrin, hemopexin, B_2-glycoprotein) or γ globulins (the immunoglobulins). Prothrombin and various other blood-coagulation factors are also glycoproteins (Clamp 1975, Putnam 1975).

Latner (1975) reported that, in terms of migration during electrophoresis mucoproteins may be α_1-globulins (orosomucoid, α_{1x}-glycoprotein) or α_2-globulins (α_2-neuramino-glycoprotein). The most abundant plasma mucoprotein is orosomucoid.

Conditions causing variation of serum glycoproteins:

Decrease in the α_1-globulin occurs in those conditions in which the serum mucoproteins are diminished, but this is not always demonstrable. These conditions are hepatocellular damage; acute hepatitis and portal cirrhosis, and certain types of endocrine imbalance. Low values may be obtained also in the nephrotic syndrome and occasionly in multiple myloma (Latner 1975).

An increase in this fraction frequently occurs in conditions characterised by increase in α_2-globulin. These are inflammatory or destructive lesions; acute and chronic infection, extensive malignancy, particularly metastatic; myocardial infarction, severe burns and other skin lesions (Gornall 1980).

Latner (1975) further reported that as regards serum mucoproteins; increased concentrations occur in a great variety of conditions associated with inflammatory, degenerative,proliferative and traumatic processes. These include acute and chronic infections, extensive malignancy rheumatic diseases, cardiovascular diseases, acute glomerulonephritis, terminal chronic glomerulonephritis (low values in nephrotic stage), and biliary obstruction. Subnormal concentrations in a patient with portal cirrhosis often rise to abnormally high levels in the presence of a complicating acute infection such as pneumonitis. Determination of the serum mucoprotein concentration may occasionally be useful in distinguishing hepatocellular (low values) from obstructive (high values) Jaundice, and in the diagnosis of the cause of hepatomegaly (low values in

hepatitis and cirrhosis; high values in metastatic malignancy). These findings have not shown much diagnostic reliability.

α_2- M A C R O G L O B U L I N (α_2-M)

Definition and biochemical properties:

α_2-M is glycoprotein with a molecular weight of 725,000. It is biologically active plasma protein, being part of a group of macromolecules which have a sedimentation rate of between 17S and 20S, and which are therefore designated 19S. All macroglobulins (including α_2-M) have a high carbohydrate content, values up to 8-11% by weight being common (Peter et al, 1977). It is relatively easy to isolate because of its large molecular weight.

The purified protein is composed of a tetramer of identical subunits of M.wt 185,000 linked in pairs by disulfide bonds. Two pairs associate by non-covalent binding to form the tetramic molecule. The subunit found to contain approximately 1450 amino acids with an amino terminal serine and a carboxy terminal alanine (Snell et al, 1983).

Plasma content:

The α_2-M accounts for between 2% and 5% of the total serum proteins at a level of 220-380mg%(Peter et al, 1977).

α_2-M = α_2 - macroglobulin.

Approximately 90% of the total trypsin inhibitory activity is due to α_1-AT, the remaining 10% is contributed by other inhibitors, mainly α_2-M and inter-α-trypsin inhibitor (Lifshitz 1980). Collagenases from skin and granulocytes are inhibited by α_1-AT, yet α_2M appears to be the most effective collagenase inhibitors in serum (Talamo 1975). Thus it might regulate the situation when excess proteinases are released from granulocytes in inflammation (Peter et al, 1977).

Proteinases bound to this inhibitor typically retain 80% - 100% of their hydrolytic activity against low molecular weight substances but only up to 10% against large proteins (Barrett 1981). Also proteinases complexed to α_2 M are not only markedly reduced in their enzymatic activity but also cleared rapidly from the circulation by cells of the reticulo-endothelial system (Imber and Pizzo 1981).

The role of α_2-M in control of coagulation and fibrinolysis have been examined. In comparison with Antithrombin III, α_2-M is a far less effective inhibitor during normal coagulation (Shapiro and Anderson 1977, Abildgaard 1979). Also recent date indicate that it can only act in a minor role, if, at all, in controlling normal fibrinolysis, the main regulator being α_2-plasmin inhibitor (Snell et al, 1983).

*The suggestion that proteinase inhibitors in

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* See also chapter of α_1-AT page 27