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A THESIS

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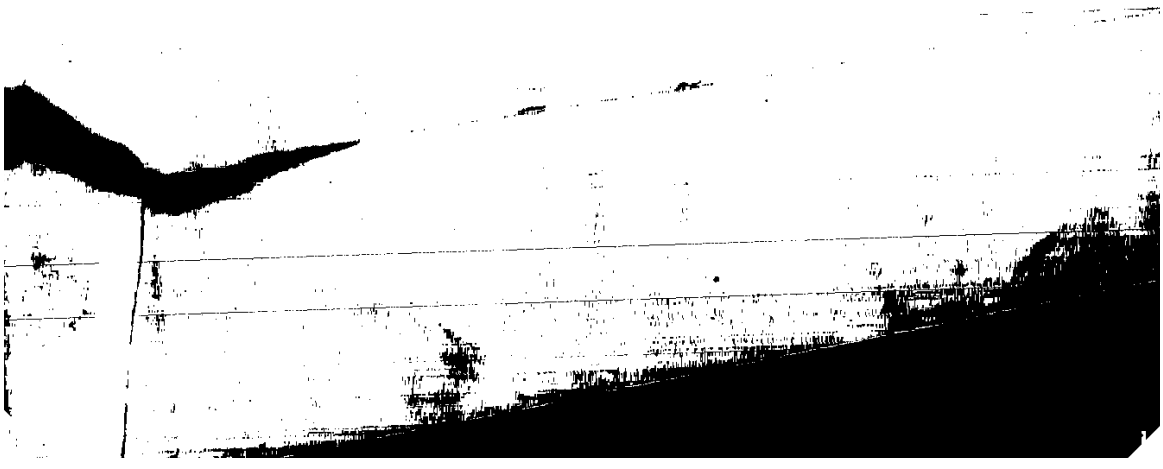
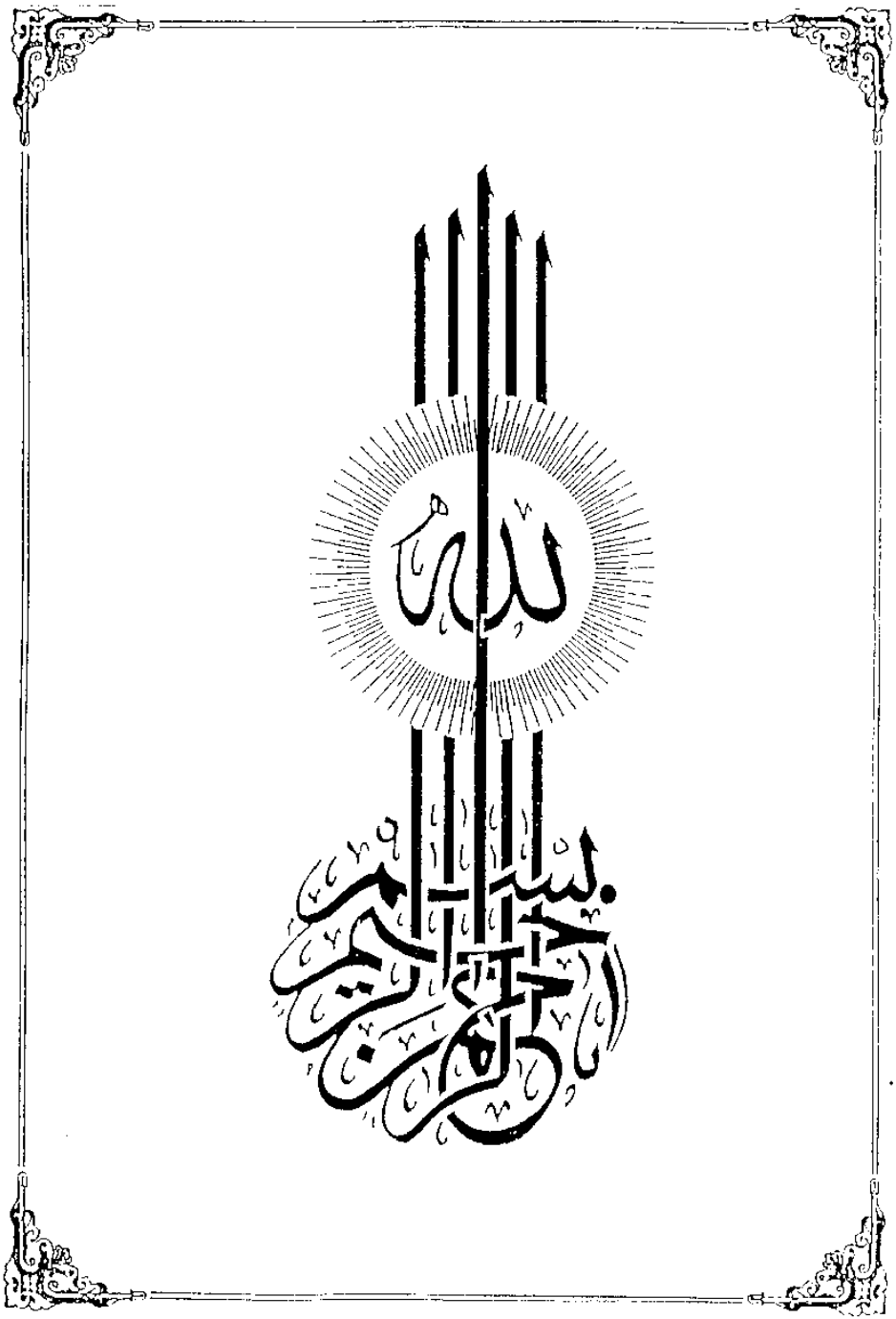
TRYPTOPHAN METABOLISM IN NORMAL, BILHARZIAL AND SOME DEFICIENCY STATES IN EGYPTIAN CHILDREN





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CONTENTS

I N T R O D U C T I O N

INTRODUCTION

There are several facts supporting the view that certain endogenous metabolites of tryptophan (O-hydroxyamines) may act as carcinogens. It has been known since 1895 by Rehn that the occurrence of bladder cancer is associated with exposure to chemicals in the dye industry. Later studies have indicated that 2-naphthylamine benzidine (Case, Hoster, McDonald and Pearson, 1954) and 4-aminodiphenyl (Melick, Escue, Naryka, Mezera and Wheller, 1956) are carcinogenic for the human urinary bladder.

Animal experiments have further suggested that the bladder carcinogens are O-hydroxyamine metabolites liberated in the urine from aromatic amines (Bonser, Clayson, Jull and Pyrah, 1952, and Bonser, Bradshaw, Clayson and Jull 1957).

Ekman and Stromback (1947), were the first to observe that patients with spontaneous bladder cancer excreted unindentified diazotizable aromatic amines in the urine, and they suggested that tryptophan metabolites might be carcinogenic.

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Cancer was induced in a significant proportion in these animals. Of these compounds 3-hydroxyanthranilic acid is the commonest and most abundant in human urine. It is also known that most of the diazotizable aromatic amines in human urine are tryptophan metabolites (Brown & Price 1956).

Urine of patients suffering from bladder cancer contains increased quantities of 3-hydroxy-anthranilic acid, 3-hydroxy-kynurenine, anthranilic acid and kynurenine (Boyland & Williams 1955).

Price, Wear, Brown, Satter & Olson (1960), also made quantitative measurement of urinary tryptophan metabolites and found that about half of the group of 41 patients with bladder cancer excreted abnormally large quantities of kynurenine, acetyl-kynurenine, kynurenic acid and 3-hydroxy-kynurenine.

Quagliariello, Tancredi, Fedele, & Saccone (1961) detected 3-hydroxy-anthranilic acid in the urine of 47 patients suffering from bladder cancer, (using peper chromatographic methods).

The association between tryptophan metabolism and cancer of sites other than the urinary bladder is not clear and many investigators have found a possible relationship between tryptophan metabolites and malignancy

at these sites. (Bonser, Bradshaw, Clayson, Jull & Pyrah (1960), Brown, Price & Wear (1955), and Price, Brown, Curreri and McIver (1955) and Price, Wear, Brown, Satter and Olson (1960).

Although industrial exposure to aromatic amines appears to account for human bladder tumours many cases occur in patients with no history of exposure to known environmental factors. However, Ekman & Strombeck(194 presented evidences that patients with spontaneous bladder tumours excreted elevated levels of aromatic amines in the urine. Similarly, Brackenridge, (1960) has found that the mean total serum tryptophan level in malignancy is significantly higher than that of normal persons.

Furthermore, it has been shown that in the dog and rat and in man, all of which are subject to carcinoma of the urinary bladder, significant amount of carcinogenic tryptophan urinary metabolites are excreted (Brown & Price, 1956); while in the cat, which does not excrete these metabolites of tryptophan in the urine, no carcinomas of the bladder were reported (Bloom, 1954). This is of more interest when one realizes that the cat

has the enzyme system required to form 3-hydroxy-kynurenine from tryptophan (Allen, Boyland, Dukes, Horning and Watson, 1957).

Furthermore, it was recently found that the cow, which in some areas of the world shows a high incidence of carcinoma of the bladder (Pamukcu, 1957), also excreted large amounts of kynurenine and 3-hydroxy kynurenine in the urine (Pamucku, Price, Brown, 1959).

Price (1958) indicated that if the tryptophan metabolites were involved in the pathogenesis of spontaneous bladder cancer, it is very unlikely that they could be a factor in more than about half of the 41 patients studied by him and he expected other aetiological factors in addition to 2-naphthylamine, benzidine and aromatic amine formed from tryptophan. Thus, the f act that only about half of the patients with bladder cancer had abnormal tryptophan metabolites cannot be regarded as evidence that tryptophan metabolites may not be aetiological factors in "Spontaneous" bladder cancer.

The fact that patients with certain other types of cancer, and patients with scleroderma, porphyria, or disseminated lupus erythromatosus have a similar type of disorder of tryptophan metabolism indicates that this response to tryptophan is not specific for bladder cancer (Price 1958).

One in fact expects, therefore, that if these tryptophan metabolites are carcinogenic, patients with scleroderma, porphyria, and disseminated lupus erythromatosus should develop bladder cancer. Since the latent period in industrial bladder cancer in man averages about 17 years (Case, Hosker, McDonald and Pearson, 1954) it is possible that patients with scleroderma, porphyria and disseminated lupus erythromatosus might not survive long enough to develop bladder cancer.

If the latent period of bladder tumour induced by tryptophan metabolites was as long as the latent period for the induction of industrial bladder cancer, the interpretation of data concerning tryptophan metabolites in the urine of patients with bladder cancer would be more difficult, i.e. it would be of interest to know the concentration of tryptophan metabolites in the urine of these patients during the 15 to 20 years before the appearance of the bladder cancer. If abnormal metabolites were due to genetic factor it would not be likely to revert to normal, however, if the metabolic abnormality due to nutritional factors, it is likely that such patients would revert to normal metabolism after suitable dietary change.

The high incidence of bladder cancer in patients with urinary bilharziasis in Egypt, Hashem (1961), Ferguson (1911), Hashem (1947) and Hashem, Zaki and Hussein (1961), Abou El-Naar (19), provided us with a unique opportunity to investigate the pattern of tryptophan metabolism in Egyptian children aged from 6 to 14 years who invariably might develop cancer of urinary bladder 20 years later on. It is quite well known that the highest percentage of incidence of cancer urinary bladder in bilharzial patients in Egypt was around the third and the fourth decade, (Makar, 1955, El-Sebai, 1961, Hashem, 1961 and El-Mofty, 1962). In Egypt, Makar (1955), Hashem (1961), reported that the maximum age incidence in bilharzial bladder cancer is in the 3rd and 4th decade while in the non-bilharzial bladder cancer in Egypt, the maximum incidence was in the 4th and 5th decades (Hashem 1961).

In European or American patients where there is no bilharzial infestation, the maximal age incidence is in the 6th and 7th decade (El-Sebai, 1961). Moreover, a history of repeated bilharzial infection of bladder often precedes the onset of cancer by an interval not less than 10 years (Hashem, 1961). Such a peculiar age distribution was explained by Hashem (1961), by the fact that the great majority of bilharzial patients contact this

disease during childhood; the disease become chronic due to exacerbation by repeated infections.

In view of the fact that changes in the pattern of tryptophan metabolism might be due to lack of nutritional elements, mainly the vitamins which act as a co-enzymes in many steps in the metabolism of tryptophan, or due to interaction of the bilharzial toxines, or the antibilharzial drugs with these enzymes, a short account on the tryptophan metabolic pathway and the influencing enzyme system concerned in the process should be discussed.

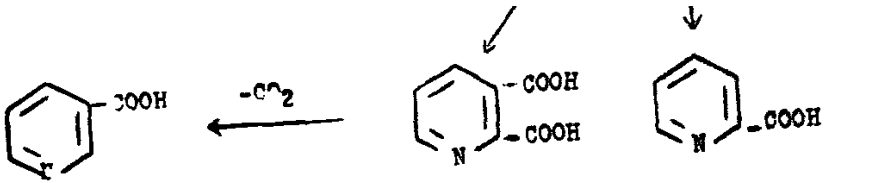
TRYPTOPHAN METABOLISM UNDER NORMAL CONDITIONS

Tryptophan is the only amino acid containing an indol nucleus - it is an essential amino acid. The metabolic pathway of tryptophan is shown diagramatically in Figure 1.

One of the main pathways for the metabolic break down of tryptophan begins by conversion of the amino acid to kynurenine. Mehler & Knox (1950) reported that kynurenine was formed from tryptophan and this reaction which was done by the liver homogenates needs O_2. The enzyme tryptophan pyrolase was involved in this direct transfer of gaseous O_2 to tryptophan. Tanako & Knox (1959) have studied this enzyme system in liver and reported that it consists of two reactions, the first produces opening of pyrole ring and oxidation of tryptophan to formyle kynurenine by the enzyme mentioned (Tryptophan pyrolase). In the second stage formyle kynurenine is hydrolyzed to kynurenine, with the liberation of formate as a bi-product.

Formyle kynurenic is rapidly converted to kynurenine so that under normal conditions formyle

(Principal catabolic pathways designated by heavy arrows).



Nicotinic acid Quinolinic acid Picolinic acid