METABOLIC ENCEPHALOPATHY

THESIS

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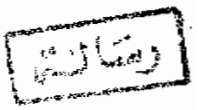
BY

NAHLA IBRAHIM ALI EL - IBIARY



UNDER THE SUPERVISION OF

PROF. DR. YOUSSEF ALI ABU - ZID
PROFESSOR OF NEUROPSYCHIATRY

FACULTY OF MEDICINE - AIN SHAMS UNIVERSITY

DR. AMIRA AHMED ZAKI DEWEDAR
ASSISTANT PROFESSOR OF NEUROPSYCHIATRY

FACULTY OF MEDICINE - AIN SHAMS UNIVERSITY

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

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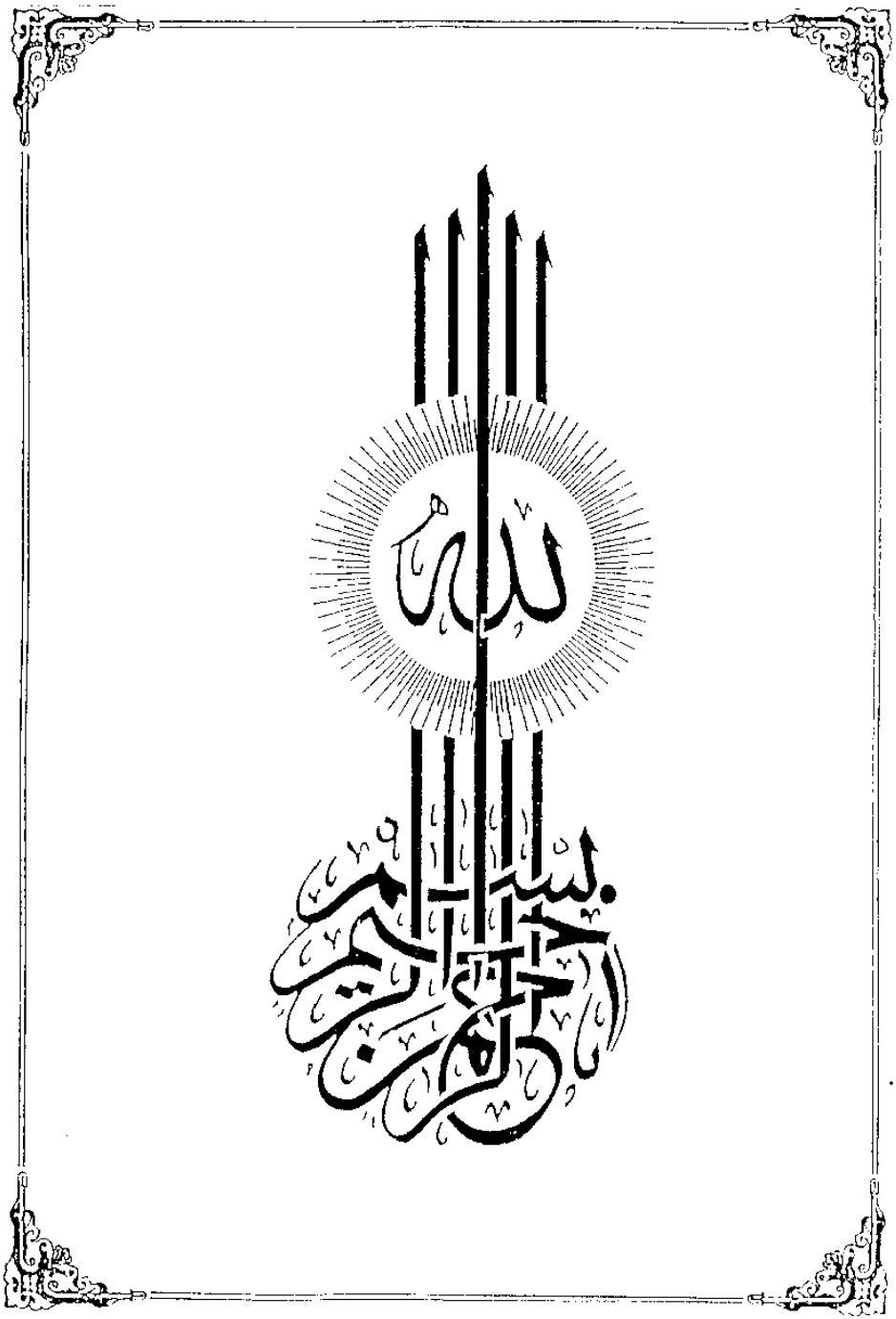
بسم الله الرحمن الرحيم

" ن والقلم وما يسطرون "

صدق الله العظيم

سورة القلم آية ١



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List of Abbreviations

- A.C.T.H. Adreno Cortico tropic hormone
- A.D.H. Anti diuretic hormone .
- A.T.P Adenosine triphosphate.
- B.B.B. Blood brain barrier
- C.N.S. Central nervous system
- C.O.P Cardiac output .
- C.P. Creatine phosphate
- C.S.F. Cerebro - spinal fluid .
- C.T. Computerized tomography .
- D.D.S. Dialysis disequilibrium syndrome .
- D.I.C. Disseminated intravascular coagulopathy
- E.E.G Electroencephalography .
- G.A.B.A. Gamma amino butyric acid
- G.A.D. Glutamic acid decarboxylase
- G.I.T. Gastro - intestinal tract
- 5 H I A.A. 5 Hydroxy indol acetic acid .
- H.V.A Homo vanillic acid
- P.D.E Progressive dialysis encephalopathy .
- P.E.T. Positron emission tomography
- R.A.S. Reticular activating system .

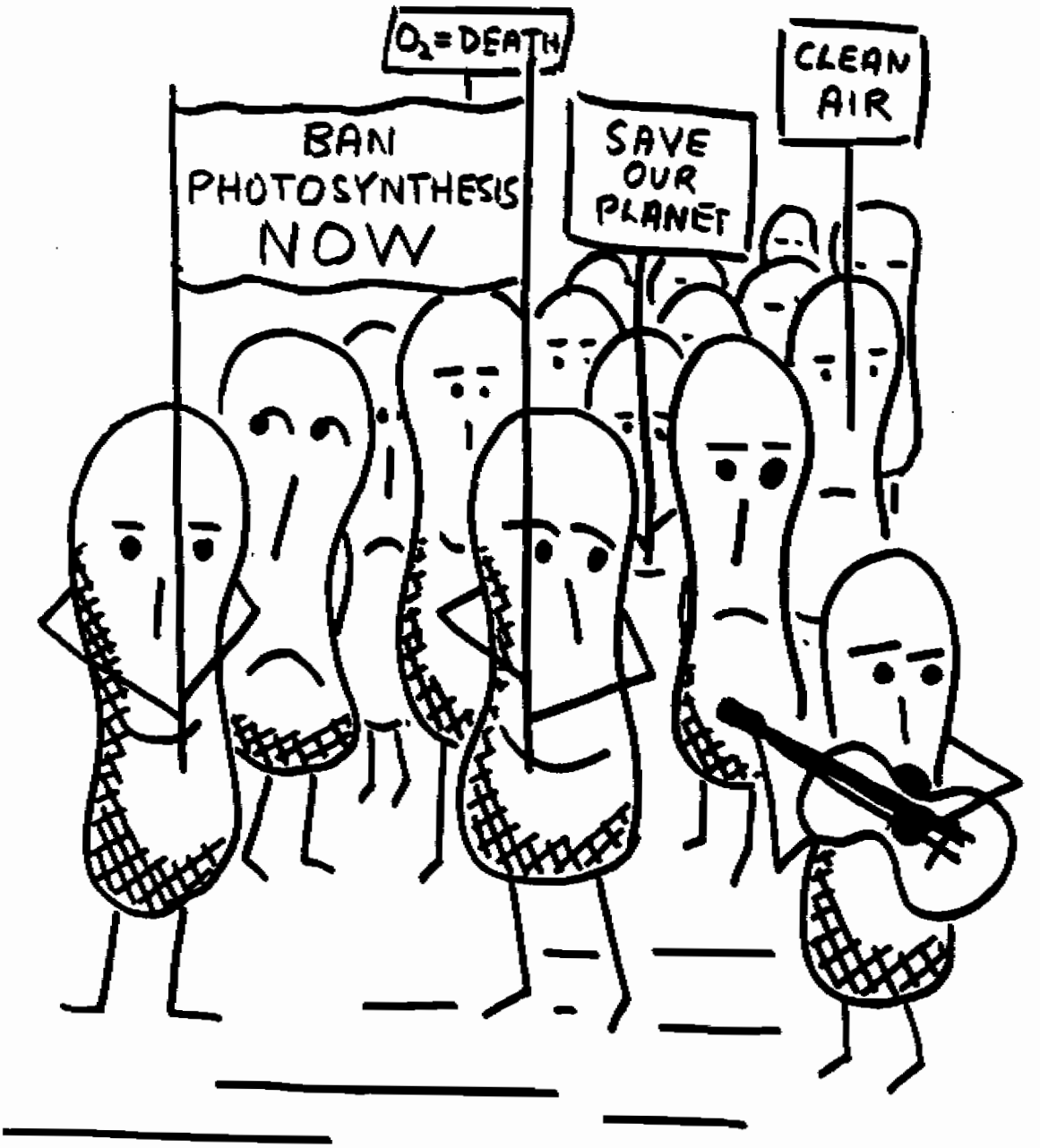

Fig. 1:

Oxygen is generally regarded "as a good gas" but see (HYPOXIA). *[hEATH, 1986]*

INTRODUCTION

CEREBRAL METABOLISM AND ITS DISORDERS

Many specific diseases, symptom complexes and syndromes result from alterations in the chemical composition or metabolic activity of the C.N.S. *[Walton, 1983]*. They represent a challenge to the attending physician in the differential diagnosis of the unconscious patient. 1980, in the study conducted by ***Plum & Posner*** about the causes of stupor or coma. Out of500 patients initially diagnosed as "Coma of unknown aetiology". 326 patients came out with a final diagnosis of "Coma due to diffuse and/ormetabolic brain dysfunction" (Plum & Posner, 1980)

When the disorder arises from an intrinsic failure of neuronal or glial metabolism i.e. Primary, it usually begins insidiously, progresses slowly and produces irreversible lesions of C.N.S. *[Plum & Posner, 1988]*. Such disorders though etymologically within the rubric of metabolic encephalopathies, but they should be excluded as they lack the acuteness and reversibility (of hypoglycaemia or uremia for example), and as they require a completely different line of treatment *[Foley, 1984]*.

When the disorder arises from extracerebral causes i.e. secondary, the resulting clinical picture will begin acutely or subacutely and often subside with time and/or treatment. This is the well established and more acceptable use of the term metabolic encephalopathy *[Plum &Posner, 1988]*. In this sens we can define metabolic encephalopathy as a term applied to the behavioural changes which result from diffuse or wide-spread multifocal failure of cerebral metabolism *[Plum &Posner, 1988]*. Or as a diffuse interference with brain function resulting from a generalized or multifocal insult that causes a wide-spread disorder in the function of neurons *[Dodson, 1984]*. The resultant clinical picture is predominated by confusion, thinking errors, behavioural abnormalities, disorders of consciousness and abnormal motor activity *[Plum &Posner, 1988]*.

Metabolic encephalopathies represent a very large area of diseases of the nervous system ranging from hypoxia and electrolyte disturbances to clinically complex disorders such as occur in liver and renal diseases *[Foley, 1984]*. Before discussing the pathophysiology of different metabolic disorders we must bare in mind some general but essential principles about normal cerebral metabolism.

1. Nutrient environment plays an important role in normal brain function *[Thomson, 1982]*. The brain consumes 25-30% of the resting metabolic rate *[Sokoloff et al., 1977]*

2. This energy is derived from oxygen and glucose which are the two essential substrates for cerebral metabolism *[McIlwain & Bachelard, 1971]*. The inability of intermediary metabolites such as pyruvat or lactate or other hexoses such as fructose or galactose to arouse patients from hypoglycaemic coma indicates that glucose can not be normally replaced in cerebral metabolism *[Bachelard, 1976]*.

3. In the resting state the brain receives about 15% of the C.O.P. This will present to the brain about 55ml blood/100 gm brain tissue/min. This amount provides the brain with about 3.5ml O_2/100gm/min, and 5.5mg glucose/100gm/min. The later is carried across B.B.B. by a process of active transport and a carrier system *[Walton, 1983] and [Mueckler, et al., 1985]*. If the blood flow, oxygen tension or glucose level fall, autoregulation start to compensate the deficit. But after certain limits this mechanism fails to keep normal cerebral metablism, and confusion and delirium appear and even coma in severe cases *[Walton, 1981]*.

4. This energy is needed for high rate of protein synthesis and also to keep Na-pump working to preserve the potential difference across the cell membrane *[Thomson, 1982] and [Fambrough, et al., 1987]*.

5. In addition the brain requires

   * Amino acids to form peptides and proteins.

   * Lipids to form myelin.

* Electrolytes to maintain impulse generation and transmission.

* Biogenic amines to form neurotransmitters. *[Walton, 1983]*.

6. Despite these needs the brain has no storage of energy and depends on continuous supplies of O_2 and glucose as well as other nutrients *[Thomson, 1982]*. And failure in these supplies result in disturbed cerebral functions up to coma *[Bachelard, 1976]*.

The different clinical syndromes produced by metabolic disorders have long been recognized empirically. But research has led to an increasing understanding of causative mechanisms. It is upon this understanding that it is now appropriate to try to lay down the foundations of a more scientific approach to these clinical problems. *[Cavanagh, 1985]*.

That will be the aim of our thesis:

1. To review the clinical pictures of these disorders stressing on the differentiating points whenever possible.
2. Understanding the possible biochemical and/or physiological mechanisms [pathogenesis] of the major causes of metabolic encephalopathies where known. This understanding is the only hope for proper management of these encephalopathies.

CONSCIOUSNESS AND ITS ALTERED STATES

"And men should know that from nothing else but from the brain came joys, delights. laughter and jests, and sorrows, griefs, despondency and lementations. And by this, in an especial manner, we acquire wisdom and knawledge, and see and hear and know what are foul, and what are fair, what sweet and what unsavory" [The Hippocratic writings 460-370 B.C.]. Since the days of the Greeks men have known that normal conscious behaviour depends on intact brain function and that disorders of consciousness are a sign of cerebral insufficiency. *[Plum & Posner, 1980].*

What is the meaning of consciousness? Consciousness is a primary element in experience and can not be defined in terms of anything else *[Walton, 1985]. Williams james* once remarked that every one knows what consciousness is until one attempts to defin it *[Adams & Victor, 1985].* However the simplest definition for consciousness is that it is the state of awareness of the self and the environment and coma is its opposite i.e. the total absence of awareness of self and environment even when the subject is externally stimulated *[Medical Research Council, 1941].* In short coma

is a state of unconsciousness which can not be reversed by normal external stimuli *[Bachelard, 1976]*.

Neurology lends support to the distinction between the content of consciousness and the state of consciousness itself *[Medical Research Council, 1941]*. The content of consciousness represents the product of thought process which depends on cortical activity. While arousal refers to the state of consciousness itself *[Medical research Concil, 1941]*. It is the other aspect of consciousness and -at least behaviourally - is closely linked to the appearance of wakefullness. It must be understood that cognition is not possible without at least some degree of arousal. On the other hand mere arousal does not garantee cognition *[Plum & Posner, 1980]*.

Arousal is mainly the function of the reticular formation *[Walton, 1985]*. The circuits of arousal in brief work as follows to keep consciousness via the thalamo cortical projection system. Non specific nuclei including the intralaminar nuclei, the septal nuclei [mid line nuclei], and the recticular thalamic nucleus will give non specific projections to the whole cortex. Their stimulation results in a widely distributed surface negative response of long latency associated with desynchronization of the E.E.G. activity i.e. more arousal *[Walton, 1981]*. And their inhibition will prodcue generalized depression of the whole