REVIEW OF LITERATURE
Nutrition and nervous system

The brain has a very high metabolic rate. Although the organ comprises 2% of the total body weight; it receives 15% of the total cardiac output. The dietary source of energy has been considered relatively unimportant for brain function under normal conditions since brain has its own mechanisms for regulating the cerebral flow and hence delivery of nutrients. It is also capable of synthesizing compounds according to its own needs. The mammalian brain requires a continuous source of oxygen and glucose to support its metabolism. Anything that interferes with the delivery of these essential nutrients will cause irreversible brain damage within minutes (Sokoloff et al. 1977). Several reports, however indicate that PCM affects the development of the human brain not only in terms of its weight and size but also with regard to the intellectual capacity (Brown 1966, Engsner & Welderman 1974, Engsner et al. 1970 a & b, Delicardo & Cravioto 1974) and that some of these changes can survive nutritional rehabilitation (Nowak & Munro 1977, Shoemaker & Bloom 1977). Prolonged consumption of protein poor diets can retard development and modify the chemical composition of brain; it may also produce long term behavioural and learning deficits ("urtman & Fernstrom
1974) and that some of these changes can survive nutritional rehabilitation (Nowak & Munro 1977, Shoemaker & Bloom 1977). Prolonged consumption of protein poor diets can retard development and modify the chemical composition of brain; it may also produce long term behavioural and learning deficits (Wurtman & Fernstrom 1974). Human and experimental PCM affect the endocrine glands, liver, intestines, blood, placenta etc. with possible secondary consequences for the development of the brain (Viteri et al. 1964, Nowak & Munro 1977).

The cells in the brain affect the growth and the differentiation of each other and alterations during an early stage will presumably influence the subsequent development (Jacobson 1978). Studies on the peripheral nervous system have revealed that a marked reduction of motor nerve conduction velocity, may occur as one manifestation of severe PCM in children (Csuntokun 1971, Sachdev et al. 1971). The reason for this reduction of motor nerve conduction velocity, which is reversible after nutritional rehabilitation, has not been clarified. Results from quantitative morphometric studies on the peripheral nerves in children suffering from PCM suggest an impaired development of medium and large myelinated nerve fibres (Dastur et al. 1977). Early nutritional deprivation has been shown to cause decreased axonal growth as well as impaired myelin deposition in peripheral nerves of the rat (Hedley-Whyte & Meuser 1971, Hedley-Whyte 1973, Sima 1974).
After severe postnatal undernutrition in rats Haltia (1970) found a decreased neuronal dry mass and RNA content in spinal anterior horn neurons. However, in pre and postnatally undernourished rats whose weights were less severely reduced, the RNA content of spinal anterior horn neurons was not significantly reduced (Sourander et al. 1976). Moderate pre and postnatal undernutrition in rats did not significantly affect the spinal ganglion nerve cell size (Olfsors & Sourander 1977).

The interaction of malnutrition and infection is well known from human pathology. Among other important factors, impaired tissue barriers have been held to contribute to the diminished resistance to infections in malnourished children (Scrimshaw et al. 1968). The perioheral nerve fibres are enveloped by tissue barriers consisting of the perineurium and the endoneurial vessel walls. It has assumed that these barriers protect the nerve fibres from toxic or infectious agents in the surrounding tissues (Thomas & Olson 1975, Kristensson & Olson 1976). Further more, this barrier function of the perineurium has been claimed to be irreversibly damaged in undernourished rats (Sima & Sourander 1973, 1974). These studies throw light on morphological, biochemical and functional changes of nervous system induced by PCM during development.
Nutrition and Cardiac System

Similarly restriction in food intake produced changes in cardiac tissue metabolism (Gold & Costello 1974). These changes are manifested by a depression in mitochondrial respiration and decrease in the activity of Krebs-cycle dehydrogenases. It has been known for a long time that changes in the metabolism of cardiac tissue can result in changes in the tissue's response to chemical transmitters. Undernutrition of protein and energy during the suckling period resulted in a lower weight of the heart and body weight and decrease in body length (Reindorf & Whitehead 1970). The heart of the undernourished animals also had fewer cells as indicated by lower DNA/heart ratio and smaller cells as indicated by weight/DNA and RNA/DNA ratios (Eckhert et al. 1975). Winick and Noble (1966) have demonstrated that the effects of nutritional status on the cellular development of body organs depend on the phase of growth during the period malnutrition is induced. In the heart, DNA synthesis continues up until day 65 postnaturally (Winick & Noble 1965). They have shown that reductions in maternal intake during the suckling period and caloric restrictions imposed after weaning, impede both myocardial hyperplasia (cell division) and hyper trophy (cell growth). If caloric restrictions are imposed after the phase of rapid cell divisions, only cell size is reduced. Refeeding after this phase will reverse the reduction in cell size but not the cell number. The importance of nutritional status on individual
cardiac cell type is unknown.

In children with Kwashiorkor radiological, electrocardiographic and pathological studies were made. Radiological and pathological evidence suggested atrophy of heart and there was clinical evidence of a low output state. A striking increase in heart size and consistent sequence of changes were found during rehabilitation. In some children electrocardiographic abnormalities persisted even after recovery (Smythe & Swanepoel 1962). In Uganda practical experience has shown that a child with Kwashiorkor should be regarded as in potential danger from heart failure (Wharton et al. 1969).

Nutrition and Gastrointestinal tract:

Most of the studies on gastrointestinal (GIT) responses were mainly on the morphological, physiological, ulcerogenesis etc. but none of the studies were directly correlated to humoral involvement in altered nutritional states. Jackson's (1915) classic experimental study was one of the first to describe atrophy of stomach and intestines after fasting. He found a total maximal loss of about 57% weight of entire gut of rats subjected to acute starvation or chronic starvation. As compared with its effects on other organs in body, fasting causes disproportionate atrophy of the small bowel in animals and man, affecting muscular and mucosal coats of the bowel (Steiner et al. 1968).
Other investigators later found that cellular size and nuclear size in the intestinal and especially in the gastric mucosa decreased with the duration of fasting and that all the layers of the intestine atrophied. Peter's (1967) detailed studies showed maximal depression of dry weight of the pylorus of rats starved for 17 days when compared to other intestinal regions. Pfeiffer et al (1966) have found that degenerative changes in the rat stomach induced by starvation depend on age; ulceration and submucosal edema are more severe in the forestomach and glandular atrophy of fundus more severe in young rats. Conversely intermittent starvation of rats is associated with gastric hypertrophy. In humans and other primates severe starvation can induce significant degeneration of the intestinal wall (Passmore 1947). Starvation or protein deprivation reduces the rate of movement of epithelial cells to villus tips in intestinal tissues and decreases overall cell renewal by 50% (Hopper et al. 1972). These kinetic changes are reflected by rapid reductions in mucosal DNA, RNA, protein, total tissue water with total number of cells (Oscarson et al. 1977, McManus & Isselbacher 1970, Altman 1972). The hypoplasia of fasting is completely reversed by refeeding (Aldewachei et al. 1975).

Small amounts of food enhance absorptive capacities of the intestines. This phenomenon has been observed with absorption of glucose, histidine, sodium and serum protein-hydrolysate in rats. The use of everted intestinal sacs
in the rat has also shown increased absorption of glucose and aminoacids during semistarvation (Kershaw et al. 1960). Improved absorption could result from larger number of epithelial cells or from an increased functional capacity of the cells. The body might compensate for partial enterectomy a condition comparable to partial starvation, in various ways (Althausen et al. 1950). However complete starvation depresses glucose absorption in man and rats. Iron absorption is also greatly depressed in starved rats (Pfeiffer 1970).

The decreased net nutrients intake appears to enhance absorption by individual epithelial cells (Dowling et al. 1967). The functional response to dietary stress is therefore distinct from that found after partial enterectomy. The weight, protein and DNA contents of enteric mucosa are 20-35% lower in rats with parenteral nutrition for 1-3 weeks than in controls receiving normal diet by mouth (Levine et al. 1974. Johnson et al. 1975). The integrity of small intestinal mucosa clearly demands the physical presence of food in the gut.

Starvation reduces the activity of intestinal enzyme activity and resulted in ulcerative and haemorrhagic lesions (Pfeiffer 1970). In many cases, infantile mortality is caused by enteric pathogens but deficiency of dietary protein is also an important cause of severe gastroenteritis (Truswell et al. 1964). Although human worm infestation, iron deficiency and protein malnutrition are often seen with intestinal malabsorptive protein repletion alone can reverse the malabsorption syndrome thus indicating the importance of this dietary factor.
AUTONOMIC NERVOUS SYSTEM

Autonomic nervous system (ANS) which as such is not a single entity, is composed of both sympathetic and parasympathetic components. It is well established that there is a balance between these components in the normal physiological processes. Nutritional factors which affect one component may also be responsible for the adjustment of the other component directly or indirectly. Many experimental parameters and potential therapeutic agents have brought to study the role of sympathetic and parasympathetic systems individually in animals and few clinical conditions. Normal dietary fluctuations of certain nutrients which contribute various precursors for neurotransmitter biosynthesis may influence the nervous system. This principle provides a new strategy for designing treatments for diseases in which correction of dietary influences may correct neurotransmitter deficiencies inherent in such disorders (Growdon & Wurtman 1970).

Concentration of neurotransmitters vary in brains of rats subjected to intrauterine and postnatal malnutrition. The variation is also reflected in litters after birth and seems to be due to fluctuations in precursors.
sympathetic nervous system

The importance of catecholamines (CA) in the regulation of metabolic processes has been recognised for over 50 years. CA influence metabolism in two ways: they increase the rate of cellular metabolism (Gale 1973, Jansky 1973, Wilmore et al. 1974, Himms-Hagen 1976) and they stimulate the conversion of complex fuels into readily usable substrate (Young & Landsberg 1977 c & d). The increased rate of cellular mechanisms induced by CA is manifested by elevations in heat production and fuel and oxygen consumption. CA stimulation of the breakdown of complex fuels supplies energy for increased cellular metabolism. Studies are undertaken to evaluate the role of sympathetic nervous system in metabolic adaptation to fasting. Fasting suppresses and overfeeding stimulates the sympathetic nervous system (Young & Landsberg 1977 a & b). During fasting, suppression of sympathetic activity conserves calories by diminishing the metabolism and heat production; during overfeeding stimulation of sympathetic activity expends calories by accelerating metabolism and producing heat. But this cannot explain many phenomena related to fasting and feeding.

The activity of the sympathetic nervous system in various physiological circumstances are assessed by measuring norepinepinephrine (NE) turnover or the rate of NE renewal, in the sympathetic nerve endings (Landsberg 1976). To measure NE
turnover, alpha methyl paratyrosine, a potent inhibitor of
tryosine hydroxylase is administered to block NE synthesis and
turnover is measured by the decline in tissue NE in symathethe-
tically innervated organs. In the other technique, (\(^3\)H) NE
is intravenously administered and taken up by the axonal
membrane amine-transport system in the sympathetic nervous
system. The rate of disappearance of (\(^3\)H) NE from a particular
tissue provides a measure of NE turnover. The activity of the
sympathetic nervous system is examined in a more direct manner,
by studying (\(^3\)H) NE turnover in the hearts of fasting rats
(Landsberg & Young 1978). Animals fasted for 48h given access
to electrolyte solution show significant decline in NE turnover
in the heart than that of control given regular diet and water.
Refeeding of 48h fasted rats restores the NE turnover to that
of control. NE turnover in the heart is more in the overfed
rats with free access to 8% sucrose solution. Similar results
are obtained in liver, pancreas and other sympathetically
innervated tissues. These findings are confirmed with the
synthesis-inhibition technique. Evidence that changes in NE
turnover represent changes in sympaetetic activity is provided
in experiments with ganglionic blocking drugs. Ganglionic
blocking drugs disrupt the flow of centrally mediated sympathetic
activity, decrease impulse traffic in the post ganglionic
sympathetic nerve endings and thus diminish release of endogenous
or (\(^3\)H) NE. The lesser effect of blockade in fasted rats and
greater effect in sucrose fed rats is consistent with reduced
impulse traffic to heart during fasting and increased impulse traffic during overfeeding with sucrose. The urinary excretion of NE is also quantitated before and after fasting. Sodium balance is also measured to ensure that volume expansion is not responsible for depression of the sympathetic nervous system. Although sodium intake increases slightly during fasting, sodium balance is not affected. Urinary NE excretion decreases significantly and comes to normal during the refeeding period. The enhanced CA excretion that occurs with refeeding was consistent with increased sympathetic activity from overfeeding.

The heat production is reduced during fasting and increased during overfeeding (Sims 1976). This has been explained in terms of thyroid hormone economy. In fasting, peripheral conversion of thyroxine to metabolically active tri-iodothyronine is diminished. Conversely in overfeeding, the formation of tri-iodothyronine is augmented. However, in view of the known effects of CA on basal metabolic rate and importance of these hormones in heat generation, it seems likely that changes in sympathoadrenal activity explains the fluctuations in metabolic rate and heat production that occurs with changes in diet. Decreased sympathetic activity will conserves calories during fasting, first as increased sympathetic activity will dissipate calories during overfeeding. It is conceivable that changes in thyroid hormone economy and activity of the sympathetic nervous system act synergistically to adjust basal metabolic rate to
caloric intake (Jung et al. 1980). If suppression of the sympathetic nervous system decreases the metabolic rate and conserves calories during experimental fasting, it presumably diminishes weight loss during therapeutic fasting or dieting. Reduced formation of tri-iodothyronine may have the same effect. Decreased thyroid and CA activity would reduce both basal metabolism and the demand for energy when the supply of exogenous fuel was reduced. Conservation of fuel and energy during fasting is clearly an important survival mechanism, and it is possible that the often questioned practice of administering amphetamines and tri-iodothyronine as an adjunct to dieting has a physiologic basis. These substances may overcome the physiologic adjustment of the organism to the fasting state, and subjects who believe that they cannot otherwise lose weight may be right. Changes in sympathetic activity may partly explain the relation between cardiovascular disease and nutrition. Increased sympathetic activity may account for some of the increased incidence of arrhythmias, angina and hypertension in populations in which over eating is common (Jung et al. 1979).

Similarly, the natriuresis of fasting may reflect an abrupt withdrawal of sympathetic activity to the kidney. CA and stimulation of the renal sympathetic nerves have been shown to cause reabsorption of sodium, independent of simultaneously induced changes in renal haemodynamics (DiBona et al. 1977, Besarab 1977). Furthermore, CA directly increases renin output
from the juxtaglomerular apparatus (Young & Landsberg 1977d).
A puzzling feature of natriuresis of fasting has been the
suppression of renin that occurs despite the impressive loss of
sodium in the urine (Boulter et al. 1974). Since CA and the
sympathetic nervous system mediate abrupt changes in renin in
many physiologic and pathologic states, the withdrawal of
sympathetic activity during fasting would explain both natriuresis
and suppression of renin release in this setting. Similarly, the
antinatriuresis or oedema of refeeding may be explained by the
direct effect of CA on sodium reabsorption by the kidney and
stimulation of renin by an increase in CA as a result of refeeding
(Landsberg & Young 1978).

Arrhythmias had been fatal in some patients during refeeding
after a therapeutic fast (Garnett 1969). In a patient with
underlying heart disease, arrhythmias could result from an abrupt
increase in sympathetic activity to the heart. Conversely, the
hypotension (Pickering 1968) and poor resistance to a variety of
pathophysiologic stresses that occur in chronic starvation may
result from suppression of the sympathetic nervous system.

The CNS discharges signals to initiate changes in sympathetic
activity in response to changes in diet. The centres that regulate
sympathetic outflow in response to changes in diet must assess
the caloric intake continually. Preliminary evidence suggests
that an insulin-sensitive region of the brain, such as the
ventromedial hypothalamus is involved in this function, since the
level of circulating insulin provides a measure of caloric intake
and functions as the major signal to other bodily tissues that calories have been assimilated (Landsberg & Young 1982).

Studies were also conducted to study the levels of CA from offsprings of well-nourished and malnourished mothers. Brains of rats whose mothers were fed 8% protein diet during pregnancy and lactation contained significantly less NE (70% of normal) and dopamine (80% of normal) at day 24 of life than brains from offspring of well nourished mothers (Shoemaker & Wurtman 1973). Normal NE levels were attained by day 90 if rats were subsequently fed on 18% lactalbumin diet; this suggests that the effects of the nutritional stress was either to delay the formation of NE synapses or to inhibit the synthesis or storage of the amine (Wurtman & Fernstrom 1974).

In general, the sympathetic and parasympathetic systems are viewed as physiologic antagonist and has been suggested that the activity of the parasympathetic nervous system can counteract sympathetic activity under some circumstances. The action of one system is easily demonstrated by surgical removal or drug induced paralysis of the opposing system. This is an interesting possibility in terms of changes in centrally mediated sympathetic activity but since there is a close usually inverse, relation between sympathetic and parasympathetic activity, parasympathetic innervation could have some role in regulation of NE turnover, particularly in the heart (Landsberg & Young 1978).
Parasympathetic nervous system

Anatomically parasympathetic nerves originate at three different levels in the central nervous axis i.e., the mid-brain, medulla oblongata and the sacral portion of spinal cord. In parasympathetic division the synapses are found close to or within the organ which the neurons innervate. The postganglionic fibres are generally nonmyelinated. When somatic nerves to skeletal muscle are severed the muscle undergoes degeneration and atrophy. Viscera which are innervated by sympathetic and parasympathetic fibres remain functionally and anatomically essentially unaltered by the severance of their autonomic innervation. The parasympathetic system is organised mainly for discrete and localised discharge and not for mass responses. It is concerned primarily with the functions of conservation and restoration of energy rather than with the expenditure of energy. It slows the heart rate, lowers the blood pressure, stimulates the out movements and secretions, aids absorption of nutrients, protects the retina from excessive light and empties the urinary bladder and rectum. No useful purpose would be served in the body if parasympathetic nerves all discharged at once (Mayer 1980).

There is surely no other compound for which a neuro-humoral function has been so well established as it is for ACh. It plays a role of paramount importance in both divisions of the ANS. The early work of Dale (1914),
Loewi (1921), Feldberg (1933) and their collaborators which first indicated the occurrence of "Cholinergic" transmission at various sites has been extensively confirmed and amplified by subsequent investigators, Dikshit (1934), a pupil of Dale, seems to be the first who on the grounds of experimental results, proposed that ACh was also a transmitter in the CNS, but convincing evidence remained sparse for a long time (Feldberg 1945). Since then, the successive introduction of new methods has increased the possibility of studying ACh metabolism and function in the CNS where its role of transmitter is now generally accepted. By means of sensitive methods for the determination of ACh and of the enzymes involved in its synthesis and degradation, the regional distribution of these substances within the CNS has been partly clarified. However, the ultimate identification of ACh in brain tissue has to await the application of gas chromatography and mass spectrometry (Hammar et al. 1968). Subcellular fractionation procedures have extended the knowledge about ACh metabolism to intraneuronal compartments. Stereotaxic methods for intracerebral application of cholinergic and anticholinergic drugs as well as refined neurophysiological technique for intracerebral stimulation and recording have facilitated investigations into the function and extension of cholinergic tracts in CNS. Also, histochemical visualization of acetylcholinesterase (AChE) as well as techniques for the determination of neuronal ACh release have been valuable tools in this field of research. Finally isotopic methods have been of fundamental
importance for studies on the synthesis, storage and turnover of brain neurotransmitter in brain. For obvious reasons most data in this basic research has been derived from animal experiments.

The sequence of events (Fig.1) which takes place during the passage of an impulse across a cholinergic pathway is as follows (Grundfest 1957):

(i) With the arrival of the nerve action potential (NAP) at the terminals of the preganglionic axon, the transmitter, ACh is liberated from the synaptic vesicles.

(ii) The released ACh diffuse across the synapse to activate the postsynaptic neuron by interacting with a muscarinic receptor on the surface of the neuron. The result of the combination produce a localised non-propagated depolarization known as the presynaptic potential (PSP).

(iii) The PSP initiates electronically a NAP which is propagated along the postganglionic fibre.

(iv) The polarised state of the postsynaptic membrane is restored with the rapid destruction of the synaptic transmitter by the diffusion of ACh away from the receptors and by the hydrolysis of ACh by enzyme AChE.

The review outlined above is not new and it has been
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2.  A.B. Libetation of ACh
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3.  ...
4.  A.P.
used or implied in part by several authors. The current hypothesis (Richelson & Elfgang 1981) is that, by combining chemically with the receptors, ACh causes the inactive effectors (Calcium channels) to become active (Fig.2). When activated, these channels open and the subsequent influx of calcium ions stimulates the synthesis of cyclic quanosine monophoshate from quanosine trichophosphate by activating the cytoplasmic enzyme quanulate cyclase. From the synthesis and turnover of cyclic quanosine monophosphate, the electrical state of the postsynaptic neuron is altered. Muscarinic receptor antagonists occupy receptor sites but do not cause activation of these receptors; hence, the calcium channels remain closed. In addition, by occupying the receptor site, antagonists prevent the action of ACh.

All cholinergic neurons contain significant concentrations of three components: Choline Acetyl transferase (ChAc), ACh and AChE. In close association with the neurotransmitter, ACh, the two enzymes ChAc and AChE are involved in its synthesis and hydrolysis respectively.

**Choline Acetyltransferase:**

This enzyme also known as choline acetylase, a basic protein with a molecular weight of approximately 65,000 was first studied in cell-free extracts of the electric organ of the Amazonian electric eel. It has been partially purified
from this and other sources by Nackmansohn (1959) and associates who have played the major role in elucidating its properties. ChAc catalyzes the final step in the synthesis of ACh—the acetylation of choline (Ch) with acetyl coenzyme A (acety CoA) (Hebb 1963 & 1972).

Acetyl CoA for this reaction is derived from pyruvate via the multistep pyruvate dehydrogenase reaction or is synthesized by acetate thiokinase, which catalyzes the reaction of acetate with ATP to form an enzyme-bound acyladenylate (acetyl AMP). In the presence of CoA, transacetylation and synthesis of acetyl CoA proceed.

Tremendous variations in ChAc activity occur in mammalian nerve tissue. In general, high concentrations have been reported for peripheral cholinergic nerves (e.g. Ventral spinal roots, Superior cervical ganglion) and thousand fold lower values are detected in afferent nerves (e.g. dorsal spinal roots, optic nerve). Similar differences have been found by ultramicro-determination of the concentrations of ChAc in single cholinergic and noncholinergic neurons of autonomic ganglia (Buckley et al. 1967). It is of interest that the human placenta, which is devoid of nervous tissue, also contains a high concentration of the enzyme.

Like other protein constituents of the neuron, ChAc is synthesized within the perikaryon and is then transported along
the length of the axon to its terminal. The synaptic vesicles may be formed at the terminal, rather than in the perikaryon (Whittaker 1959). In addition to the vesicles, the axon terminals contain a large number of mitochondria, where acetyl CoA is synthesized as described. Ch is taken up from the extracellular fluid into the axoplasm by active transport. The final step in the synthesis probably occurs within the cytoplasm, following which most of the Ach is sequestered within the synaptic vesicles (Potter 1972). Moderately potent, selective inhibitors of ChAc are available (Cavallito et al. 1960).

**Acetyl Cholinesterase**

Body fluids and tissues contain enzymes, initially called cholinesterase (ChE) that rapidly hydrolyse Ach and butyro-cholinesterase (BuchE). AchE, also known as "specific" or "true" ChE occurs in neurons, at neuromuscular junctions, and in certain other tissues; it is responsible for the hydrolysis of Ach released in the process of cholinergic transmission. BuchE also known as serum esterase, "nonspecific" or "pseudo" ChE is present in various types of glial or satellite cells but only to a limited extent in neuronal elements of the central and peripheral nervous system and in the plasma, liver and other organs; its physiological role is unknown. AchE hydrolyses Ach at a greater velocity; BuchE on the other hand exhibits maximum velocity of hydrolysis with butyrylcholine as substrate.
It is possible to visualise by histochemical techniques, the sites of enzyme activity in relation to the various structural components of tissues and cells (Koelle 1975). Such studies have shown that neurons that give rise to the three categories of peripheral cholinergic fibres (postganglionic parasympathetic, preganglionic autonomic and somatic motor) contain relatively high concentrations of AchE throughout their entire length of cholinergic neurons (Koelle 1951 & 1955). The concentrations in noncholinergic peripheral neurons (adrenergic, primary afferent) are, in general, considerably lower, but there are marked species variations. A small percentage of sympathetic ganglion cells in most species contains concentrations of AchE equivalent to those of their respective parasympathetic ganglion cells; evidence has been obtained that in the ChAc, the former cells give rise to the cholinergic sympathetic fibres that innervate the sweat glands (Sjoqvist 1963).

**Acetylcholine**

**Synthesis of Ach**: Ach is synthesized by combination of Ch and acetyl CoA catalysed by the enzyme, ChAc (Berg 1956). This process takes place most actively in the region of axonal terminals, where ChAc is at its highest concentration.

ChAc is a cytoplasmic enzyme and acetyl CoA is a mitochondrial product (Deduve et al. 1962). The source of Ch in nerves is either by uptake system from Ach hydrolysis
FIG:3. SYNTHESIS, STORAGE & RELEASE OF ACh
IN NERVE TERMINALS (BUR AND 1973).
or by carrier mechanism from plasma Ch (Bligh 1952). Sources outside nerve terminals by carrier mechanism can be inhibited by hemicholinium and its analogues (Chang & Lee 1970, Potter 1970, Seakens & Stoll 1965).

Storage of Ach: (Fig. 4) The total Ach content is stored in a releasable depot form, which is subdivided into more readily and less readily releasable reservoirs. The remaining Ach is in a stationary form not released by nerve impulses and is perhaps located centrally to the axonal terminals. An additional surplus portion that may exceed the total depot Ach accumulates in the presence of an anti ChE agents (Hubbard 1973).

Release of Ach: It is certainly released in a quantal form.

Quantal form: It comes from the available fraction of the releasable stores. As the presence of surplus stores does not directly influence quantal release, it cannot come from these stores (Potter 1970).

Non-quantal form: Ach is spontaneously released in a form not detected as AP or NAP is supported by the experiments of Mitchell and Silver (1963). It is not surprising that isolated nerves can release Ach upon stimulation, both from their cut ends and from the injured portion between the ends.

In addition to its numeral transmitter role, Ach has been proposed to act at the terminals of adrenergic fibres to
FIG. 4. STORAGE OF ASH IN A SHOE TERMINAL (HUMMAD 1973).
facilitate the release of NE (Bum & Rand 1950), of various neurosecretory (Konstantinova 1967), and noncholinergic fibres of the CNS to promote the release of their transmitters (Koelle 1961) as well as at certain cholinergic terminals as a positive feed-back of ACh release amplification mechanism.

Choline in ACh synthesis (Fig: 5)

Many workers have found that Ch availability in the brain directly influences the rates at which cholinergic neurons synthesize and release their neurotransmitter, ACh (Cohen & Wurtman 1975 & 1976). Ch is the physiologic precursor for ACh (Schuberth et al. 1960). Its administration increases blood Ch, brain Ch and brain ACh in rats and blood and cerebrospinal fluid Ch in human beings (Growdon et al. 1977). The enzyme, ChAc which catalyses Ch to ACh, is not fully saturated with either of its substrates under physiologic conditions. Thus increase in the amount of Ch available to the enzyme accelerates ACh formation although the mammalian brain can generate free Ch from the break down of phosphatidylcholine in cell membranes and from de novo synthesis, the efflux of Ch from brain to blood, which depends on Ch concentration gradient across the blood-brain barrier. (Pardridge 1977), eventually would deplete brain Ch levels were it not for dietary contributions to the plasma Ch. Blood Ch actually derives from two major sources: some is synthesized in the liver by the step-by-step methylation of ethanolamine to form phosphatidylcholine (lecithin) and some is obtained from dietary sources, mostly in the form of lecithin (Bremer &
FIG:5. CChL AND CHEMICALS.

Greenberg 1961). Lecithin is the naturally occurring source of dietary Ch. In addition lecithin may be more acceptable to patients since it does not have the bitter taste or fishy odour associated with Ch ingestion. Foods with a high lecithin content include eggs, meat, fish and legumes (Goodhardt & Shils 1975). Lecithin also is used as an emulsifier in processed foods and is consumed by a large but indeterminate segment of the population as capsules or granules sold in health food stores. About half of the lecithin consumed probably enters the thoracic duct intact. The rest appears to be broken down to glycerophosphorylcholine in the gut mucosa and then to Ch in the liver. Plasma Ch levels in humans normally vary over a two- or three-fold range, depending on the quantities of lecithin consumed in the diet, (Hirsch et al. 1978). Thus, when six normal subjects ate a diet containing less than 50 mg of Ch base per day and for two days, plasma Ch levels did not fluctuate. Subsequently, when the same subjects consumed three isocaloric meals containing a total of 5 g of Ch base (as lecithin) daily for two days plasma Ch levels rose three-fold after the first meal of the day. Free Ch is transported into the intact brain by a low affinity uptake system, located at the blood brain barrier, similar to the system for the neutral aminoacids (Pardridge 1977). Fortunately this system is distinct from the high-affinity Ch uptake system in cholinergic nerve terminals, which is nearly saturated at normal plasma Ch levels and thus would be relatively unresponsive
to food-induced changes in plasma Ch. Since both the brain-uptake system and ChAc are highly unsaturated, any significant variation in plasma Ch levels might be expected to generate corresponding changes in brain Ch and Ach levels. This expectation was realised when Cohen and Wurtman (1975 & 1976) and Haubrich et al. (1975 a & b) reported that administration of Ch by injection or by dietary supplementation increased blood Ch, brain Ch and brain Ach levels in rats. Furthermore, Ch injected as lecithin, its naturally occurring source, was even more effective in elevating serum Ch levels in human and brain and adrenal Ach levels in rats (Hirsch et al. 1978). The increase in neuronal Ach levels produced by Ch administration probably causes a corresponding increase in the amounts of Ach increased at the synapses when neurons are depolarized. In addition, dependence on Ch availability seems to become even more important when cholinergic neurons are firing rapidly. The relationship between dietary Ch consumption and brain Ach synthesis thus fulfils the criteria for precursor control.

Variation in Ach

ACh plays a key role in the transmission of nerve impulses (Nachmansohn 1961). It has been suggested that concentration of ACh in the brain varies inversely with the functional activity of the brain, such as it has been found to be increased in anaesthesia and sleep (Richter & Crossland 1949, Crossland & Merrick 1954), in deep narcosis (Elliot et al. 1950) and
following the administration of CNS depressants (Naik et al. 1970 b). Concentration of ACh in the brain was found to be decreased during convulsions, electrical stimulation of brain and emotional excitement, (Richter & Grossland 1940). Different types of stress also modify brain ACh content. A reduction in ACh level in brain and heart was observed during spinning stress (Naik et al. 1970 a), cold stress (Sharma & Parmar 1967), hypothermia (Anand et al. 1959) and electrically induced convulsion (Richter & Grossland 1940) whereas an increase was observed during foot electroshock stress (Dube et al. 1972) and restraint stress (Sharma & Barar 1966). The concentration of ACh in the brain also increases with the age (Grossland 1951, Naik et al. 1970 a). Dietary fluctuations may be important for the synthesis of neurotransmitters which contribute to regulation of both neuroendocrine response and behaviour (Anderson 1981). The availability of choline to brain influences the rate of synthesis of ACh (Growdon & Wurtman 1970). Naik et al. (1970 a) have reported increase in ACh content on rat brain during various periods of acute starvation.

It is generally accepted that during the neonatal period when brain is rapidly developing, undernutrition may interfere with normal maturation as judged by brain weight, DNA and lipids (Winick & Noble 1966, Dobbing 1968). An increase in the concentration of ACh associated with maturation led Rajalakshmi et al. (1974) to study the effect of undernutrition, severe undernutrition and protein deficiency with caloric
restriction. Concentration of brain ACh in rats was unaffected by undernutrition during neonatal period but was found to be decreased by both severe undernutrition and protein deficiency during the post-weaning period. Antipsychotic drugs such as chlorpromazine have been shown to either stimulate the neuronal release (Stadler et al. 1973) and turnover of ACh (Trabucchi et al. 1974) or to reduce its concentration (Sethy & Van 'Oert 1974, Guyenet et al. 1975) in the corpus striatum suggesting that such drugs increase the activity of cholinergic neurons in this region of the brain. It did not affect the concentration of ACh in the cortex. In contrast clozapine lowered the level of ACh in both corpus striatum and cortex (Haubrich et al. 1975 a).

Variation in ACHE

Undernutrition on growth, size and composition of rat brain has been studied by various groups of workers. (Culley & Lineberger 1046, Guthrie & Brown 1068, Winick 1075). ACHE activity is affected by a variety of factors such as age, nutrition, surgical interference, irradiation etc. (Silver 1074). ACHE activity of rat brain was found to decrease during various periods of acute starvation and after administration of CNS depressants. (Naik et al. 1070 a & b) ChE levels are high in the younger age and gradually become stable at adulthood (Naik et al. 1070 a). ACHE was retarded in suckling rats whose mothers had a restricted food intake during pregnancy and lactation (Adlard & Bobbing 1071 a & b). The levels of ACHE in the developing brain was depressed by undernourishment but
reached normal values once ad libitum feeding was allowed (Sereni et al. 1966). Dams underfed from 7th day of gestation to 21 days postpartum were thereafter fed ad libitum. All the young ones were weaned at 25 days of age and fed ad libitum thereafter until maturity. AChE/μg/h rose by 14% but AChE/whole brain/μg/h failed to show any difference (Adlard & Dobbing 1971 a & b). Severe malnutrition, especially protein-caloric restriction early in the life of experimental animals can cause behavioural abnormalities which persist long after nutritional rehabilitation (Russell 1960). Im et al. (1971) fed lactating dams on inadequate protein during suckling to decrease milk production but during pregnancy they were fed ad libitum. After a 3 week nursing period young ones were weaned to a low protein diet for the next 4 weeks. Severe protein-caloric deficiency in early life resulted in long lasting increases in the brain ChE activity. Like ACh, seasonal and time of day can influence AChE. In some clinical conditions like carcinoma (Vaccarezza & Willson 1965, Vaccarezza et al. 1969), tuberculosis, anaemia and liver diseases, ChE levels are lower, whereas in diabetes, asthma (Vaccarezza & Peltz 1960) and hyperthyroidism ChE levels are higher. Smyth & Beck (1960) showed that the initial effect of alcohol was to decrease the level of brain CoA; later ACh, ChAc and AChE levels also fell. Sideman et al. (1965) showed higher serum ChE levels in spastic children.