MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

April 15, 1965

HEPATIC ENCEPHALOPATHY

Definition: Clinical syndrome of (1,2,3,4)

1. Abnormal mental state with
   a. Disturbed consciousness
   b. Personality changes
   c. Intellectual deterioration
2. Abnormal neuromuscular state
3. Liver disease
4. Characteristic, but nonspecific, laboratory and EEG findings

Clinical Syndrome

1. Abnormal mental state

   a. Disturbed consciousness:

      Sommolence and inversion of sleep rhythm
      Fixed stare
      Apathy
      Slowness of response (especially late in day)
      Stupor $\longrightarrow$ coma (in children and patients with viral hepatitis may see delirium)

   b. Personality changes:

      Euphoria
      Irritability
      Loss of concern for family
      Inappropriate behavior

   c. Intellectual deterioration:

      Slight impairment of mental function $\longrightarrow$ gross confusion
      Inability to carry out simple calculations (subtraction of serial 7's)
      Constructional apraxia (difficulty in writing and reproducing simple designs with blocks and matches)

2. Abnormal neuromuscular state

   Asterixis (See characteristics in detail - Page 2)
   Slurred speech
   Perseveration
   Grasping, incoordination
   Ataxia
   ↑ DTR's early, ↓ or absent DTR's late

Hoffman and/or Babinski (often unilateral and transient)
Ankle clonus
Rigidity (even appearance of decerebration)
Choreoathetosis
Hyperventilation
Coma (at first arousable) → lack of response to any stimuli (loss of corneals)
Convulsions (especially in children and with acute liver disease)
Irreversible spastic paraplegia rarely - 6 cases (5,6).

"Asterixis" - (metabolic flap) (7)

a. Movements consisting of lateral deviations of fingers and flexion - extension at metacarpo phalangeal and wrist joints. Best seen with arms outstretched, wrist hyperextended and fingers separated. Absent at rest, mitigated by intentional movement and maximal on sustained posture. Usually bilateral, often asynchronous. At intervals of fraction of second to a few seconds.

b. May be seen on sustained contraction of other muscles (protrusion of tongue, dorsiflexion of foot).

c. Associated with electromyographic periods of electrical silence. Believed due to inappropriate integration of afferent stimuli normally transmitted by ascending (?extrapyramidal) tracts to brain stem reticular formation (8).

d. Not specific (9). Seen in uremia, severe pulmonary disease with heart failure, barbiturate intoxication, hypomagnesemia, etc.

3. Liver Disease - Failure of parenchyma and/or of hepatic circulation. "Essential" for development of encephalopathy (10).

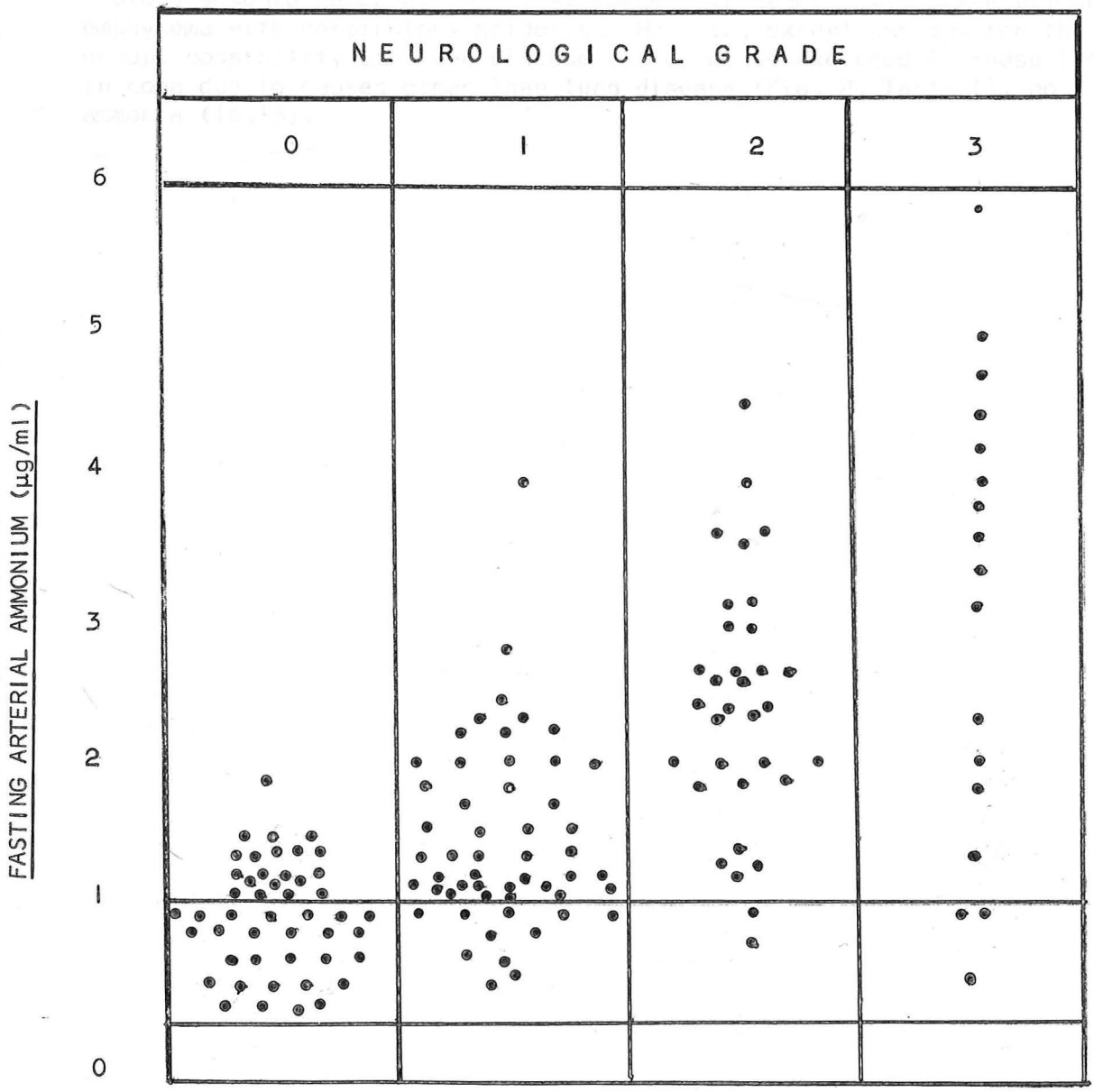
Fetor hepaticus - Seen in 46% of one series (11). Sweetish musty smell. Believed due to methyl mercapton (CH_3SH) or dimethyl sulfide ($CH_3S:SCH_3$) - both abnormal derivatives of methionine which accumulates in blood of patients with liver disease (12). Not seen in non-hepatic encephalopathy

4. Laboratory and EEG findings

a. Laboratory:

Blood: (1) ↑ ammonia concentration, especially arterial. (See Figure 1 - Page 3)

Figure 1 (13)



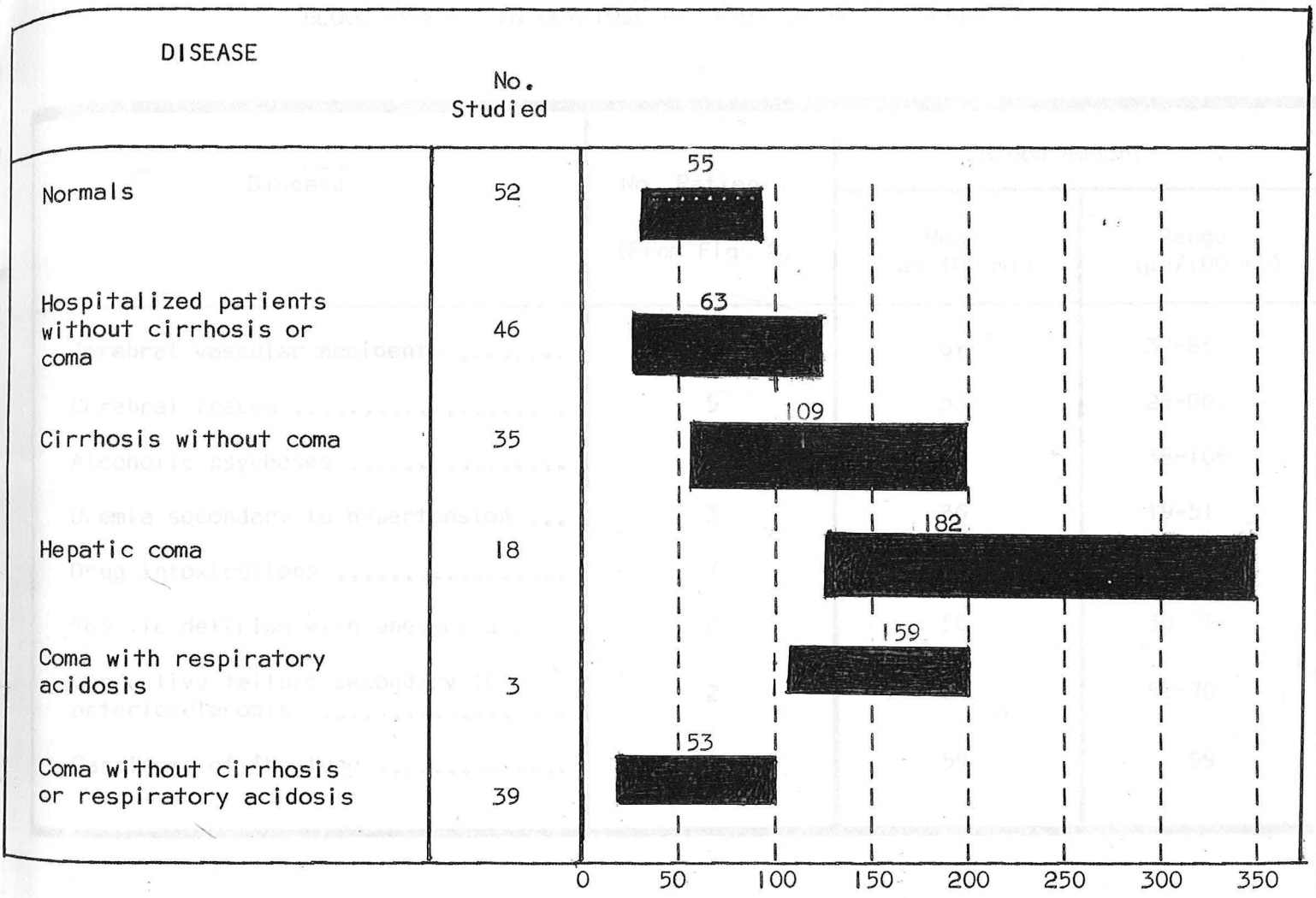
The relation of the arterial ammonium level to the grade of consciousness in hepatic cirrhosis.
Grade 1: minor disorder of consciousness and the motor system.
Grade 2: gross disorder of consciousness with disorientation in time and space.
Grade 3: coma. Mean normal arterial ammonium level is 0.68 µg/ml. The horizontal lines denote mean ± 2 S.D.

Mean values in patients with impending or fully developed hepatic coma are elevated. However 10 - 25% of arterial samples (Figure 1) and 25 - 50% of venous samples may be in normal range in individual patients and there is often no good correlation in patients with liver disease between degree of cerebral abnormality and ↑ in ammonia (13,14,15).

↑ blood ammonia reported in shock, congestive heart failure and pulmonary emphysema with respiratory acidosis. However, except perhaps for the last group, possibility of liver disease could not be excluded in these instances. In coma due to causes other than lung disease (Fig. 2, Table 1), no ↑ in ammonia (16,15).

Figure 2 (16)

BLOOD AMMONIA IN µg/100 ml (venous)



The range and mean of blood ammonia levels. (Figures above bars indicate mean values.)

Table I

BLOOD AMMONIA IN COMATOSE PATIENTS WITHOUT CIRRHOSIS

Disease	No. Patients Studied (From Fig. 2)	Blood Ammonia	
		Mean (µg/100 ml)	Range (µg/100 ml)
Cerebral vascular accidents	11	61	37-85
Cerebral trauma	5	53	26-86
Alcoholic psychoses	8	64	38-106
Uremia secondary to hypertension ...	3	36	19-51
Drug intoxications	7	57	34-79
Febrile delirium with pneumonia	2	50	30-71
Congestive failure secondary to arteriosclerosis	2	64	52-70
Carcinoma of the lung	1	59	59

(2) Amino acids: α-ketoglutaratic, pyruvic, acetoacetic, methionine, tyrosine, phenylalanine, asparagine, glutamine (17,18). Less correlation with neurologi state than ammonia. Probably related in part to impaired metabolism by diseased liver.

CSF:
1. ↑ ammonia, α-ketoglutarate, pyruvate (14)
2. ↑ glutamine (Table II) of diagnostic value (17,18,19,25)
3. Normal or ↑ protein - no ↑ in cells or pressure (20)

Table II

GLUTAMINE LEVELS IN CSF (19)

	Hepatic Coma	Cirrhosis	Other Liver Pathology	Other Comatose States	Control Cases
No. of cases	26	17	18	21	98
Range (mg%)	23-96	13-30	6-24	6-19	5-22
Mean ± S.D. (mg%)	52 ± 17	21.3 ± 4.2	15 ± 5.2	11.4 ± 3.7	10.3 ± 3.5

b. EEG:

Paroxysms of bilaterally synchronous, symmetrical, high voltage, slow waves at 1 - 7 cycles/second (normally 8 -13/second). Start anteriorly and progress posteriorly (21).

Abnormality of most significance in precoma. However, although on average EEG abnormality correlates with neurologic disorder, there is overlap (in both directions) in individual cases.

EEG (especially in full coma when it is diffusely slow) is not specific for hepatic encephalopathy. Abnormalities seen in anoxia, uremia, hypoglycemia, diabetic coma, etc., (22), - non-specific.

Electronic frequency analysis detects early cases (23,24), especially after administration of protein or small doses (8 mgm) of morphine (24).

Diagnosis

1. Clinical syndrome (present in full or in part).

2. Exclusion of other causes: hypoglycemia, subdural hematoma, etc.

3. Confirmation by response to therapy is helpful.

Pathogenesis

1. Consciousness (wakefulness, awareness, reactivity): Depends on functional integrity of reticular activating system in brain stem. This polysynaptic network (rete) of neurons receives and correlates afferent stimuli from within and without the body (26,27). Cortex apparently is not essential, but may modify consciousness(28). Rigidity, asterixis and hypernea, often present in hepatic encephalopathy, also are believed to depend on structures located in brain stem (29).

2. CNS pathology in hepatic encephalopathy

a) Early: None
b) Few days: ↑ number and size of protoplasmic astrocytes in brain gray matter. Probably specific, but may be seen in hypoxia (30). Occasionally - demyelination of pyramidal tracts in spinal cord (5).

Conclusion: Absent or scant anatomic changes and reversibility of clinical picture suggest a metabolic disorder.

3. CNS physiology in hepatic encephalopathy (31,32,33)

See Tables III and IV on pages 9 and 10.

Table III (32)

Cerebral Metabolism in Hepatic Disease

	Mean CBF (ml blood/100 g brain/min	Mean $CMRO_2$ ml O_2/100 gm brain/min	Mean A-V O_2 (Vol. %)
Normal	54.0	3.3	6.0
Alert	47.1	2.3	5.1
Moderate cerebral dysfunction	41.9	1.7	4.4
Coma	39.6 (↓ 26%)	1.6 (↓ 50%)	4.1

CBF = cerebral blood flow
$CMRO_2$ = cerebral oxygen consumption
A-V O_2 = arterio--venous oxygen extraction

Table IV (33)

Cerebral Metabolism in Hepatic Disease

Degree of Neurologic Impairment	CBF* ml/100 g/min	$CMRO_2$* cc/100 g/mm	A-V O_2* Vol. %	Pa CO_2 mm Hg	Art. pH	Art. O_2 Sat %	PO_2 mm Hg
Normal (11)†	53	3.4	6.6	38	7.42	95.2	89
Grade (6) 0-1	59.0	3.4	5.9	33	7.48	90.0	57
Grade (9) 2	47.0	2.8	6.1	29	7.51	93.0	64
Grade (6) 3	36	2.0	5.6	30	7.55	89.5	55
Grade (3) 4	22	1.6	7.2	25	7.57	92.0	56

* See footnote Table III
† Number of subjects

Summary of findings in Tables III and IV:

1. Progressive decrease in cerebral oxygen consumption ($CMRO_2$) with increasing neurologic impairment.

2. Decrease in cerebral blood flow (CBF), possibly, at least partly, a result of drop in Pa CO_2 (from hyperventilation).

3. Respiratory alkalosis common (Table IV).

4. In general, $CMRO_2$ more depressed than CBF, and cerebral oxygen extraction ($A\text{-}VO_2$ not sufficient to compensate for ↓ CBF.

5. (?) Decreased cerebral glucose uptake (34) (inconstant).

Comment: Cause or effect?

Decreased $CMRO_2$ occurs in other states of decreased consciousness, as uremic coma, diabetic coma, etc., and is not specific for hepatic encephalopathy (35). However, it does not invariably follow states of sommolence - i.e., normal in sleep and pentathol semi-narcosis (35).

Probability; Hepatic coma is result of ↓ $CMRO_2$, which may, however, be common denominator of other metabolic disorders.

Conclusion: Impaired cerebral oxidative metabolism, possibly associated with faulty glucose utilization.

Postulated causes of disturbed cerebral metabolism in hepatic encephalopathy:

I Toxin

a) ammonia
b) methionine and/or other nitrogenous products
c) tryptophane metabolites (indoles)

in conjuction with

II Sensitivity of brain in liver disease, possibly as result of depletion of vital substances (? cytidine, ? uridine) (36) synthesized by normal liver.

Ia) Ammonia Toxicity

Evidence in favor:

1) ↑ ammonia levels in blood and CSF of patients with hepatic coma.
2) Precipitation of syndrome in susceptible patients and animals by administration of ammonia or substances (blood, proteins) giving rise to it.
3) Frequent alleviation of syndrome by therapeutic measures which prevent ammonia influx into brain.

Evidence against:

1) Lack of precise correlation in individual patients between degree of neurologic impairment and level of blood or CSF ammonia.
2) Much higher levels of ammonia (than in patients with coma) are necessary to produce coma in experimental animals and to demonstrate toxic effect (↓ O_2 consumption) of ammonia on brain in vitro (37).

Comment - re: Evidence against

Blood and CSF levels do not necessarily reflect intracerebral concentration of ammonia. Blood ammonia measurement is notoriously difficult and subject to error (45). Blood pH is an important variable - at ↑ pH, NH_3 transfer into brain augmented (2).

Animal and in vitro studies are short-term (minutes-hours) experiments and do not take into account presence of a sensitized brain.

Conclusion:

Arguments against ammonia as a cause of hepatic encephalopathy do not seem convincing.

See Table V on page 13

Table V

Ammonia Metabolism in Health and Hepatic Encephalopathy

	NORMAL METABOLISM	METABOLISM IN HEPATIC FAILURE
Sources		
Gut:	Effect of bacterial and (?) digestive enzymes on proteins and urea.	↑ NH_3 from a) intestinal bleeding b) ↑ BUN c) high protein diet
Kidney:	Deamination of glutamine and amino acids with release of NH_3 into renal veins.	↑ NH_3 - from diuretics (chlorothiazide, Diamox) which alkalinize urine and may cause hypokalemia
Muscle:	Release on exercise-(?) from adenylic acid.	↑ NH_3 - released from muscle saturated with ammonia-(?) mechanism.
Removal Mechanisms		
Liver:	a) urea synthesis (Appendix I) b) glutamine synthesis (See Fig. 3)	NH_3 - removal impaired probably due to decreased urea and glutamine synthesis by diseased liver and ammonia shunted around liver by portosystemic shunts.
Lung: (minor)	Exhalation	May be ↑ with hyperventilation and ↑ blood levels of NH_3.
Muscle: (liver)	a) amination of keto acids α - ketoglutaric acid ↓ NH_3 glutamic acid (ATP) ↓ NH_3 glutamine b) carbamyl phosphate synthesis (Appendix I)	May be impaired since ketoacids ↑ in blood

Conclusion: Ammonia ↑ in hepatic encephalopathy due to its increased production (exogenous type) and/or decreased metabolism (endogenous type). Often "mixed" type seen.

Importance of pH for ammonia metabolism (38,39,40,41,42,43,44,45)

Ammonia in body fluids exists as NH_4^+ and NH_3, and proportion of each component is dependent primarily, on pH, as shown below for plasma at 37°C.

$$pH = pKa + 10\% \times \frac{NH_3}{NH_4} \qquad (\sim 2\%)$$

(7.40) (8.90)

Current methods estimate total ammonia ($NH_4 + NH_3$) but only NH_3 freely crosses tissue membranes. NH_4^+ diffuses very slowly, probably because of its water solubility and charge.

With ↑ blood pH, the proportion of NH_3 in blood rises, resulting in a larger quantity of gaseous ammonia which can enter into the brain. The NH_3 distributes itself between the 2 compartments on basis of pH gradient, tending (as a weak base) to move from alkaline to acid side, i.e., from blood to relatively more acid intracerebral milieu (pH~ 7.0). Any ↑ in blood pH (without equally altering cerebral pH in some direction) will augment transfer of NH_3 into brain. (This assumes the same pKa for ammonia in both sites).

Thus, metabolic alkalosis will increase plasma NH_3 and will enhance transfer of ammonia into more acid intracellular sites (brain). This explains why alkalosis (viz. diuretic (Diuril) induced) may be detrimental in hepatic encephalopathy.

Evidence of this is abundant from animal experiments where wide pH shifts can be employed (39,40,41,42,43) and less evident (but still convincing) in human studies where lesser pH changes are tolerated (44,45,46).

Respiratory alkalosis in hepatic encephalopathy (33) - (See Table IV

Etiology unknown.

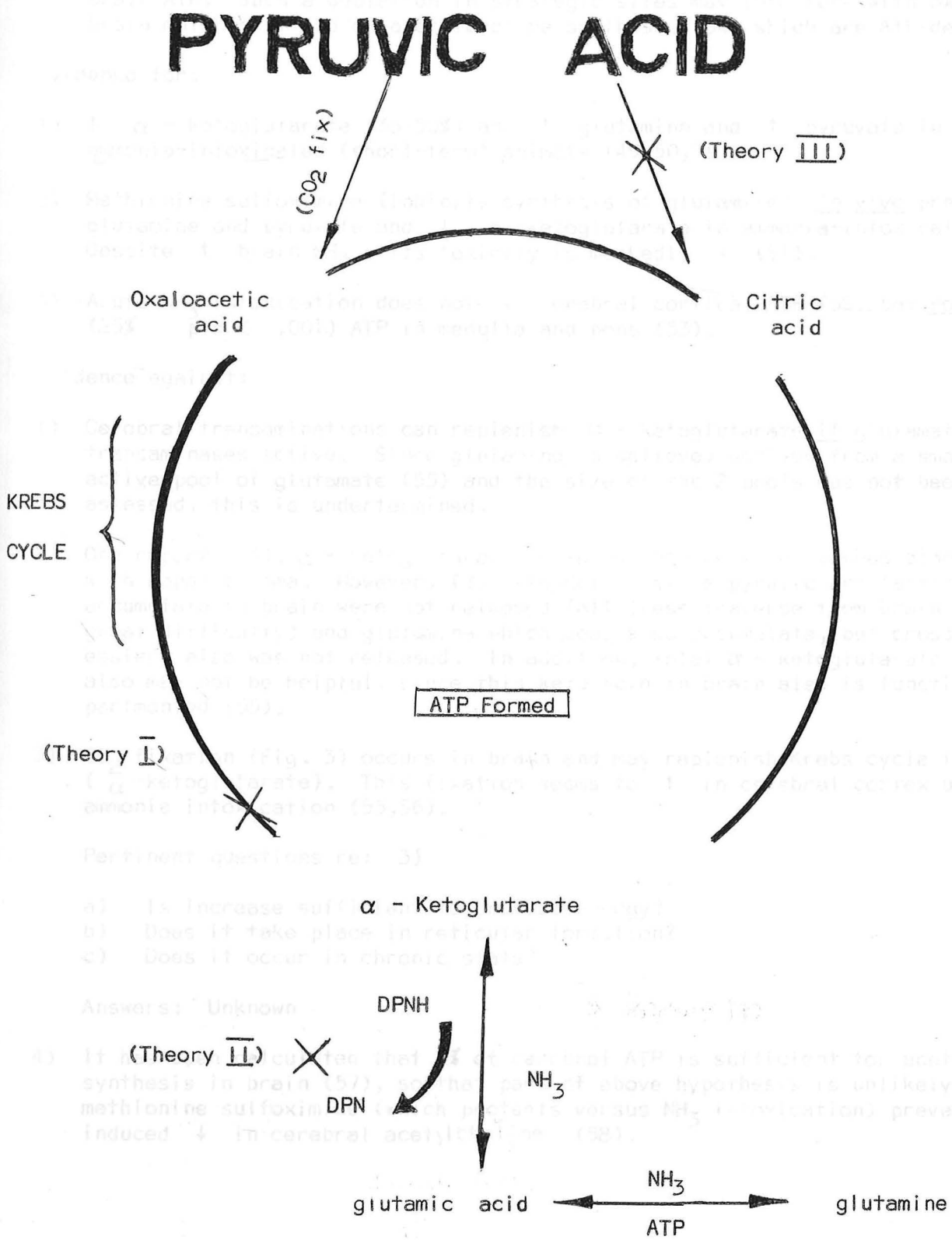
Theories:

a) Stimulation of peripheral lung reflexes: - no evidence available
b) Effect

   1) Due to ↑ ammonia: - conflicting data (47,48)
   2) Compensatory for intracerebral accumulation of acid metabolites: - no evidence available.

Figure 3

MECHANISM(S) OF AMMONIA "TOXICITY"



Theory I Cerebral α- ketoglutarate depletion (Bessman) (49)

Principle: Increased brain ammonia is detoxified to glutamine with resultant depletion of α - ketoglutarate which cannot be replinished from blood since it does not readily cross the "blood-brain barrier". Decrease in α - ketoglutarate slows Krebs cycle and this together with consumption of ATP to form glutamine depletes brain ATP. Such a depletion in strategic sites may interfere with oxidative brain metabolism and/or acetylcholine synthesis (54) which are ATP-dependent.

Evidence for:

1) ↓ α - ketoglutarate (35-50%) and ↑ glutamine and ↑ pyruvate in brain of ammonia-intoxicated (short-term) animals (49,50,51).

2) Methionine sulfoximine (inhibits synthesis of glutamine) <u>in vivo</u> prevents ↑ glutamine and pyruvate and ↓ α -ketoglutarate in ammonia-intoxicated animals. Despite ↑ brain NH_3 - its toxicity is markedly ↓ (51).

3) Acute NH_3 intoxication does not ↓ cerebral cortical ATP (52) but <u>does</u> ↓ (25% $p =< .001$) ATP in medulla and pons (53).

Evidence against:

1) Cerebral transaminations can replenish α - ketoglutarate <u>if</u> glutamate adequate and transaminases active. Since glutamine is believed derived from a small metabolically active pool of glutamate (55) and the size of the 2 pools has not been separately assessed, this is undertermined.

2) One report (34), α - ketoglutarate released into cerebral venous blood in patients with hepatic coma. However, (?) methodology since pyruvic and lactic acids which accumulate in brain were not released (all these traverse from brain to blood with great difficulty) and glutamine which does also accumulate, but crosses into blood easier, also was not released. In addition, total α - ketoglutarate measurement also may not be helpful, since this keto acid in brain also is functionally compartmented (55).

3) CO_2 fixation (Fig. 3) occurs in brain and may replenish Krebs cycle intermediates (α -ketoglutarate). This fixation seems to ↑ in cerebral cortex under acute ammonia intoxication (55,56).

Pertinent questions re: 3)

a) Is increase sufficient to provide energy?
b) Does it take place in reticular formation?
c) Does it occur in chronic state?

Answers: Unknown

4) It has been calculated that 1% of cerebral ATP is sufficient for acetylcholine synthesis in brain (57), so that part of above hypothesis is unlikely. Interestingly, methionine sulfoximine (which protects versus NH_3 intoxication) prevents an ammonia-induced ↓ in cerebral acetylcholine (58).

Theory II Decreased supply of DPNH for ATP generation in mitochondria as result of competition for DPNH by α- ketoglutarate $\xrightarrow[NH_3]{DPNH \longrightarrow DPN}$ glutamate reaction.

(Worcel and Ercinska) (61)

Principle: DPNH oxidation necessary for generation of ATP by mitochondrial electron chain.

Evidence for:

1) In vitro data shows that NH_3 inhibits O_2 uptake by mitochondria and this is proportional to formation of glutamate from α- ketoglutarate. This cannot be prevented by addition of excess - ketoglutarate so depletion of this ketoacid is not causal; succinate as substrate (which does not depend on DPNH) is not affected by NH_3; addition of DPNH to α- ketoglutarate prevents toxic ammonia effect.*

2) Results in vivo with methionine sulfoximine (51) and studies on brain ATP (53) could go along with this theory.

Theory III Impaired oxidative decarboxylation of pyruvic acid. (McKhenn and Tower) (59)

Principle: Pyruvic (and possibly α-ketoglutaric) acid's entry into Krebs cycle via citric acid is impaired - with slowing of cycle.

Evidence for:

1) In vitro data shows that mitochondrial O_2 consumption is impaired to a degree as pyruvate utilization was decreased. This was not remedied by adding succinate, DPN. Mechanism of action unknown.

Evidence against:

1) Contradicted by another study utilizing similar methods (61).

2) Not supported (as sole cause) by in vivo data with methionine sulfoximine.

3) Authors neglect own data on α- ketoglutarate that support Theory II.

Theory IV Direct toxic effect of ammonia on neurons.(Weil-Malherb) (60)

Principle: Interference of NH_3 with ionic flux across neuronal membranes.
No data to support this.
In vivo methionine sulfoximine data (51) suggest that intracerebral ammonia increase per se cannot explain the whole effect of NH_3.

Conclusion: Theories I and II, perhaps in combination seem most tenable.

* Glutamine reverses the effect of ammonia by preventing ammination of α-ketoglutarate. The level of TPNH has also been shown to be depresses (70%) on addition of ammonia (104).

I
d) Methionine and Other Amine Toxicity

Evidence in favor:

1) Methionine, its metabolites and other amines may be elevated in blood, urine, and CSF of patients with hepatic coma (62).

2) Administration of methionine may precipitate coma in susceptible patients (63).

3) Methyl mercaptan (by-product of methionine) induces unconsciousness (5 mg/per l. inspired air) in rats (64).

Evidence against:

1) Methionine I.V. is <u>not</u> toxic in patients in whom coma is precipitated on oral administration (64).

2) Rx with oral antibiotics prevents above toxicity.

3) Portal vein ammonia ↑ after giving methionine (65).

4) Monamine oxidase inhibitors prevent rise in blood ammonia after infusion of ammonium citrate, suggesting that amines (derived from aminated ketoacids) may be source of ammonia (66).

<u>Conclusion:</u> These data suggest that methionine and its products, as well as other amines may precipitate hepatic encephalopathy but a likely mechanism is via release of ammonia. No other specific mechanisms have been postulated.

I
c) <u>Tryptophan metabolites (indoles) toxicity (64)</u>

Theory a) Depletion of cerebral serotonin, due to inability of liver to convey tryptophan to 5-OH tryptophan, the precursor of serotonin.

Evidence in favor:

1) Serotonin is present in high concentration in brain stem and may be concerned with normal and abnormal brain function (67).

2) 5-OH indole acetic acid (5HIAA) (end product of serotonin) may be decreased in urine of patients with severe liver disease (67).

3) Administration of 5-OH tryptophan I.V. to patients with hepatic coma, but not other types of coma, improved their EEG (68).

Evidence against:

1) Importance of brain serotonin as related to signs of hepatic coma is debatable (67).

2) Lowered urinary excretion of 5-HIAA in liver disease not confirmed (69).

Theory b) Tryptophan is converted by gut bacteria to indole and skatole. Small amounts of these enter the circulation and in presence of liver disease and/or collateral circulation may not be conjugated as sulfates and glucuromides for urinary excretion and thus may accumulate in blood as toxins.

Evidence in favor:

1) Indoles and skatoles *in vitro* at high concentrations inhibited respiration of brain (37).

Evidence against:

1) Such high concentrations of these substances not found in man (37).

Conclusion: Not enough evidence to assess the role of tryptophan metabolites in human hepatic encephalopathy.

II ↑ Sensitivity of the brain in hepatic disease

Evidence in favor:

1) Normal individuals with high blood ammonia levels (maintained by I.V. infusion) were asymptomatic. Note, however, that these are brief infusions (hours) (70). In presence of alkalosis, ammonia in large doses was toxic in "normal" individuals (71).

2) Patients with liver disease and especially those with encephalopathy are very sensitive to hypoxia, CO_2, sedatives, etc., - all of which excerbate neurologic impairment (9).

3) Isolated perfused cat brain loses its electrical excitability in absence of liver in perfusion circuit. The liver can be substituted for by inclusion of cytidine and uridine (36).

4) Respiration of brain from animals with chronic liver disease is more depressed by toxins (ammonia) *in vitro* (37).

Conclusion: Evidence strong that liver disease may sensitize brain to various toxins.

Summary on Pathogenesis of Hepatic Encephalopathy

1. Metabolic cerebral disorder with decreased oxygen consumption.
2. Occurs in individuals, with liver disease (parenchymal and/or circulatory hepatic impairment), whose brain is sensitive to a variety of "toxins" which often summate in their deleterious effect.
3. "Toxins" very likely include ammonia and other nitrogenous products. Hypoxia, electrolyte disturbances, alkalosis, etc., - often potentiate this effect.
4. Precise site of action of "toxins" is not known but appears to involve Krebs cycle, probably at level of α- ketoglutarate.

Therapy

I. Standard - of established value.

1. Removal of precipitating causes and treatment of their effect.
2. Stop influx of nitrogenous substances into body (stop or decrease ingested protein, antibiotics, etc.).
3. Maintain caloric, fluid and electrolyte balance.

II. Semi-Experimental - of possible or probable value.

1. Arginine
2. Glutamate
3. Removal of colon from continuity of intestinal tract.
4. Steroids

III. Experimental - unproven value.

1. Urease immunity
2. Hemodialysis - peritoneal dialysis - resin dialysis - cross circulation
3. Cation exchange resins
4. Protamine

TABLE VI (72)

I.

1. Removal of precipitating causes and treatment of their effects.

Incidence:

Provoking Causes of Coma in 167 Cirrhotic Patients with Coma (1958-1962)

	Cause	%
1.	Gastrointestinal hemorrhage (varices 57%)	37
2.	Progressive hepatic failure (no "external" precipitating cause)	19
3.	Diuretics (paracentesis 10%)	17
4.	Unknown	14
5.	Infection	10
6.	Uremia	2

TABLE VII

Cause	Mechanism(s) of Coma Precipitation
1. Hemorrhage*:	a) ↑ ammonia and other nitrogenous products (100 ml blood = 15-20 gm protein)
	b) Decreased hepatic and kidney function, the latter resulting in ↑ BUN → NH_3
	c) Ammonia in banked transfused blood (73); storage at 4°C - 1 day = 170 µg%; 4 days = 330 µg%; 21 days = 900 µg%
	d) Shock and hypoxia
3. Diuretics:	a) ↓ [K], alkalosis - resulting in ↑ intracellular transfer of NH_3, ↑ ammonia released from kidneys (74,75)
	b) Paracentesis - may lead to oligemia and ↓ renal function with ↑ BUN and sometimes dilutional hyponatremia
	c) (?) Unknown effects - possibly on uptake of "toxins" by peripheral tissues.
5. Infection (septicemia, peritonitis): Mechanism unknown	
Possible causes:	a) ↑ tissue catabolism with ↑ endogenous nitrogen load
	b) Dehydration with decreased renal function
	c) "Toxicity" - hypoxia (76), hyperthermia (77).
6. Uremia:	a) Effect of disease itself on brain
	b) ↑ BUN → NH_3
7. Sedatives**: Anesthetics:	a) Effect on brain oxygen consumption
	b) Hypoxia

Excessive protein ingestion is special case of 1.a

* Morphine and other sedatives absolutely contraindicated in hepatic coma.

For Rx of delirium tremens - promazine drugs (used in judicious doses) probably best.

For Rx of convulsions in hepatic coma - barbital, phenobarbital, which are excreted largely via kidneys. Reduced dosage employed, and patients Rx titrated by clinical response.

For surgery - minimal anesthesia compatible with procedure.

2. Stop influx of nitrogenous products.

a) In coma stop protein ingestion completely.

In precoma - decrease protein ingestion to ~ 40 gm/day.

b) Antibiotics to decrease gut bacterial flora.

Generally used - non-absorbable antibiotics - neomycin, paramomycin.

Initial Rx of coma - 8 gm/day in divided doses. Subsequently, 3-4 g/day. In precoma 1-2 gms/day may be adequate (minimal dose not well established.)

At 8 gm/day - Stool E. coli essentially disappears in most patients in 2 days; may see ↑ in yeast, diptheroids, strep fecalis (78,79). Fetor hepaticus usually disappears in 3 days, paralleling decrease in blood ammonia (78). Clinical condition of patient usually (but not always) improves in 36-72 hours, but may take a week.

In patients with ileus, neomycin may be given as 1% enema in water. Most ammonia is produced in colon (80) and enemas have resulted in ↓ blood ammonia in dogs and man (81). The reliability and consistency of response to this procedure in man are not definitely established.

Relative value of other blood spectrum antibiotics (tetracyclines, chloramphenical) vs. neomycin is not well established clinically. In dogs they have a lesser effect than neomycin on bacterial flora and suppression of ammonia production (80). There is suggestive evidence that they are also less effective in patients (103). Note that intravenous tetracycline (and other antibiotics excreted in bile) may not be adequately excreted into gut in presence of liver disease (Schenker and Combes, unpublished observations).

Caution: Neomycin is absorbed slightly (1-3%) and may accumulate in blood (ototoxic, nephrotoxic) in patients with renal failure.

Neomycin may lead to malabsorption syndrome - apparently dose-time dependent and probably due to direct effect of drug on gut mucosa (82).

Neomycin may cause staphylococcal enteritis by suppressing endogenous microbial flora, therefore, with diarrhea - stools must be smeared and stained for diagnosis and immediate treatment.

c) Constipation (retention of gastrointestinal blood) must be prevented by judicious use of enemas and laxatives. Excessive (routine) use of former may precipitate dehydration and augment any disturbance of electrolyte status and the latter may be detrimental in patients with gastrointestinal bleeding.

3. Caloric, fluid and electrolyte balance.

On withholding of protein, patient must receive at least 1600 calories as glucose. After 2-4 days of antibiotic therapy, gradual reinstitution of protein (starting with 25 gm/day) has not been detrimental to patients (83). Some wait until evidence of improvement before starting protein. Protein intake is titrated vs. clinical response. Finally, antibiotics are gradually stopped. Best to vary one factor at a time.

Proof of value of above regimen.

a) No strictly controlled study.

b) Immediate mortality in patients prior to above therapy = ~ 90% (83). Present immediate mortality in comparable patient population = 40-50% (84).

c) Prognosis best if precipitated by exogenous factor(s) which can be reversed. Worse with "unprovoked" liver failure, high bilirubin, low [Na] (84).

II. Semi-Experimental Therapy

1. Arginine -

Principle: Serves as substrate for urea cycle (Appendix)

Comment: Not established that there is a hepatic deficiency of arginine. Furthermore, arginase decrease in cirrhotic liver has been demonstrated (85) and this may limit usefulness of arginine.

Variable results obtained in practice. Better in patients who may recover spontaneously and worse in those with poorer prognosis. One controlled study (86) failed to show effect on either clinical state or blood ammonia. However, the dose used may have been too low - one infusion of 25 gm/2 hours. Some claim good results with larger doses.

Arginine may lower blood ammonia when given as HCl salt due to ↓ pH.

2. Glutamate -

Principle: a) Combines with NH_3 ⟶ glutamine by transamination

b) Yields α - ketoglutarate which takes up NH_3.

Comment: Glutamine is eventually deaminated with release of ammonia. Most studies show no consistent value. Only controlled study showed no benefit using single infusion of 25-50 g/2 hour (87).

3. Colonic Exclusion -

Principle: Removal of site of "toxin" formation.

Comment: This approach has been used only for patients who:

a) Do not respond to trials of protein restriction plus antibiotics, on assumption that a sufficient number of gut bacteria are resistant to therapy.

b) Do not follow prescribed therapy and are in danger of becoming mental cripples.

c) Become protein depleted (↑ ascites) on restricted diet

This approach has on occasion given excellent results (88,89,90). It should definitely be considered in the proper patient, who is not a forbidding surgical risk, prior to development of irreversible neurologic abnormalities.

4. Steroids -

Principle: Unknown. In hepatitis may decrease inflammatory response.

Comment: Most studies (91,84) show no beneficial effect in cirrhosis but an occasional one (92) claims temporary improvement with massive (1000 mg cortisone/day). None are controlled.

In viral hepatitis, coma outcome almost always fatal (93). Although no strict control studies available, therapy with cortisone 500 mg g 8 h (or equivalent doses of prednisone, etc.) was associated with recovery (93) in some patients (9/23 = 39%). Improving prothrombin time serves as only good guide to prognosis. Two patients had perforations of ulcer and one bled from intestinal tract - out of 23. Therapy with steroids is now recommended for viral hepatitis, pending further data.

III. Experimental

1. Urease immunity (94,95,96)

Principle: Immunize with jackbean urease, induce antibodies to urease which pass into intestinal content and inhibit bacterial intestinal urease with resultant decrease in ammonia production.

Comment: Immunization with urease has given ↑ serum antiurease antibody levels (94) and with use of under 8 units of urease no toxicity. Of 8 patients with recurrent encephalopathy - in 6, tolerance for protein increased markedly (100-300%) without increase in blood ammonia levels (95). In animals there was a 60% ↓ in gastrointestinal urease, - in gastrointestinal ammonia and antibodies to urease present in feces.

However,

1) Study not well controlled.
2) Three patients developed coma after immunization with 10-20 units - ine one this may have hastened death.

3) Blood ammonia levels were not decreased in any patient.

4) Two of eight patients failed to respond despite high serum antiurease antibodies.

5) Antibodies may be rapidly digested in gut (96).

Conclusion: Needed:

a) Further control studies
b) Measurement of antiurease in human gut content

2. Hemodialysis, exchange dialysis (97) -

Principle: Remove circulating ammonia and other toxins via artificial kidney, resin column, etc.

Comment: Hemodialysis may effectively remove ammonia (20 mg in 4 hours (98) but procedure is tedious, often rendered dangerous by need for heparinization and difficult to apply to large number of patients. Peritoneal dialysis may be of value, expecially with concommitant renal failure, but no control studies are available.

Scattered reports available concerning use of resins and one of parabiosis (99). Although some benefit is claimed - insufficient data is available at present.

3. Cation exchange resins (100-101) -

Principle: Orally administered exchange resins (exchange Na or K for NH_4) bind NH_4 in gut lumen and thus remove it.

Comment: Excellent results obtained in dogs given blood p o - substantial decrease in blood ammonia (100). In patients with gastrointestinal bleeding, equally good results obtained (101). Use of resin in K cycle may bind ammonia and replete body K which is often low in cirrhotics. Serum electrolytes and ECG monitor necessary. Resin may be given by enema also.

Dose suggested: 20 grams in 30 ml 70% Sorbital q 6 h p o.

4. Protamine -

Principle: Basic protein consists of 80% arginine - may slowly release arginine into circulation.

Comment: In experimental animals, protamine lowers blood ammonia (102). Insufficient data for human studies. In large doses drug is an anti-coagulant.

Conclusion regarding therapy:

Standard therapy indicated under I has proven of value. In special instances therapy indicated under II (semi-experimental) may be beneficial. Other procedures are strictly in investigative stage.

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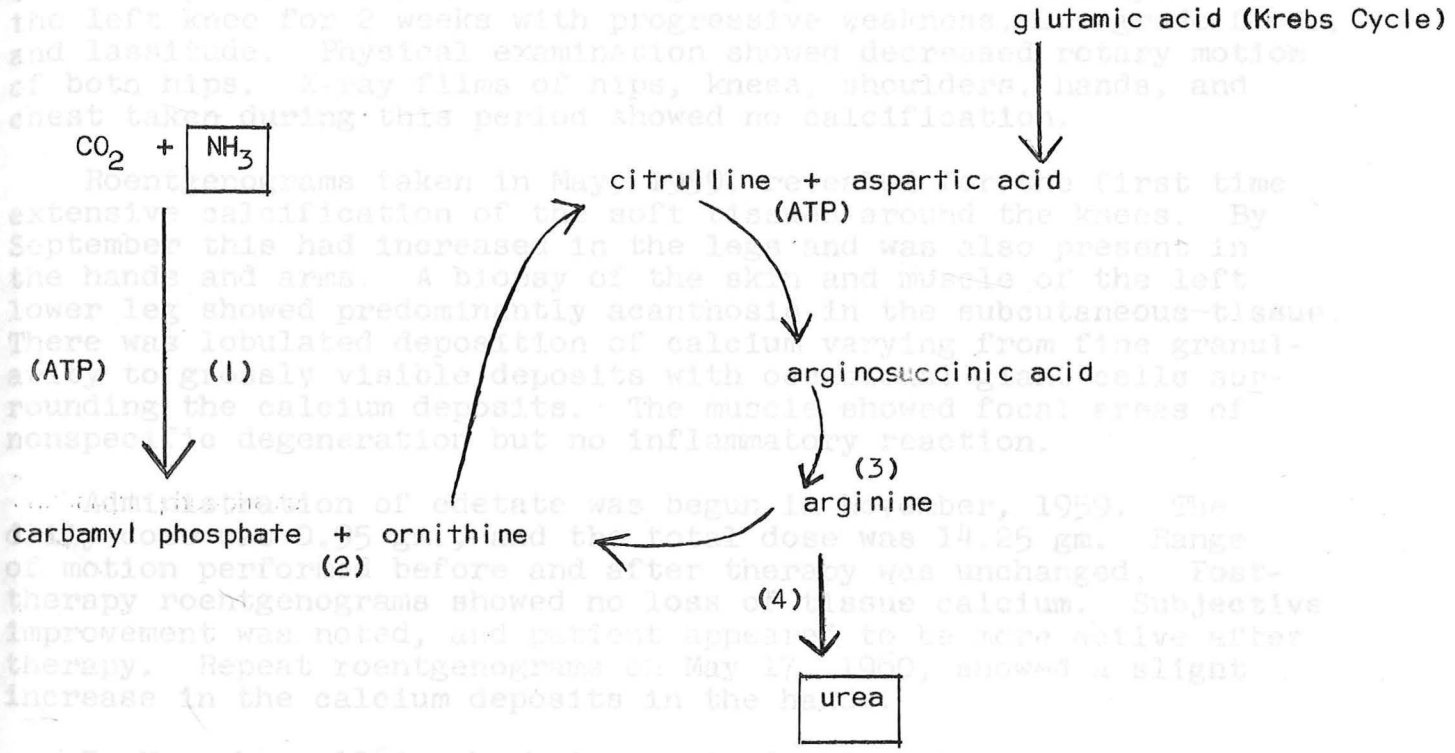
Appendix I

U R E A S Y N T H E S I S



Urea Cycle Enzymes

(1) carbamyl phosphate synthetase

(2) ornithine transcarbamylase

(3) arginine synthetase (condensing and cleavage)

(4) arginase