1955

Hepatic coma : a review

Paul W. Saltzman
University of Nebraska Medical Center

HEPATIC COMA

-a review-

Paul Wesley Saltzman

Submitted in Partial Fulfillment for the Degree
of Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1955

Omaha, Nebraska

(appendix II)

TABLE OF CONTENTS

INTRODUCTION

When the subject of hepatic coma is brought up among an average group of physicians, one cannot help but notice the perplexed, puzzled and often totally blank response such comment illicits from the group. Actually, the reasons for this lack of uniform responsiveness are neither clear nor acceptable, and it is in this light that such a topic presented itself to this author.

Both Hippocrates and Galen recognized and were familiar with the disturbed mental function that often attends jaundiced patients. Although hepatic coma has been recognized as an ominous complication of hepatic disease for over one and one-half centuries, little progress in the understanding and therapy of this comatose state has been advanced until recently. It is the purpose of this thesis to review and attempt to clarify recent developments in liver coma and, in the end, it is hoped that the interested reader may add to his store of knowledge while the passive examiner may, at least, gain some familiarity with this disease process. An attempt will be made to present the etiologic factors as well as the generally recognized important signs and symptoms connected with hepatic coma. A brief survey of pathological findings and a rather complete, and it

is hoped, understandable discussion of the biochemical and metabolic processes will be undertaken. Finally, a summary of the latest developments in the therapeutic approach to this syndrome will be given. Interspersed throughout will be commentary and opinions of this author. It must be admitted that the author's clinical experience is limited, particularly as concerns this topic.....no actual case studies are reported on in this thesis. Yet it would seem that the attempt at an honest appraisal of the literature, perhaps uncolored by personal feelings and dogmatic concepts, would serve of some value and tend to approach the level of understanding and interest of those for whom this work is primarily intended.

ETIOLOGY AND PRECIPITATING CAUSES

Not too infrequently, the contributing factor ushering in a state of coma is overzealous therapy on the part of the attending staff. Surgical procedures may precipitate hepatic coma in severe parenchymal liver disease. Also, in such conditions, excessive sedatives and narcotics are probably contraindicated. Too vigorous fluid therapy, indiscriminant paracentesis with subsequent Na loss, and injudicious use of ammonia salts or ammonia forming substances are among other iatrogenic causes of hepatic coma (Butt-1). Common unpredictable etiologic factors are severe hemorrhage, hypotension, localized or systemic infection, recent alcohol debauch and generalized worsening of the liver condition.

Hepatic coma may occur in the acute or active and the chronic or stabalized liver disease. In a recent detailed study by Karl et al (2), 58 cases of hepatic coma were classified, there being only one survival. Men were markedly prominent in the group, the average age being 54.6. 40 cases gave a history of poor nutrition, 50 cases gave a history of use of excessive alcohol. In 16 patients, near starvation appeared to precipitate the onset of coma, while 12 patients indulged in a recent alcoholic debauch.

NEUROPATHOLOGY

Pathological studies of central nervous system tissue in fatal hepatic coma have generally yielded little well-substantiated information and consist of non-specific findings which have given little aid in unraveling the mysteries of liver coma. Post-mortem studies are infrequently reported in the literature, probably because of the paucity of findings and the emphasis on the biophysiologic aspects of this disease process. It is to be emphasized that the syndrome of hepatic coma is primarily that of a biochemical and physiological nature, affecting basic body metabolism rather than anatomical structures per se.

Adams and Foley (3), in a rather complete review of the neurlogical processes associated with hepatic coma, discuss the autopsy findings on their large series of cases. The gross examination of the brain revealed little of import. The most prominent microscopic change was the enlargement and increase in the number of protoplasmic astrocytes in all parts of the cerebral cortex, brain stem nuclei, lenticular and dentate nuclei....this finding differed significantly from that found in the non-comatose group with advanced liver disease. Severe cases showed degeneration of the nerve cells in the cortex but, generally, only minor alterations were found in the

brain parenchyma. Little correlation was found between the number and size of the astrocytes and the severity of the disease, although these changes were probably one of the most distinctive attributes of hepatic coma, as concerns neuropathology. These findings also were found to occur in Wilson's diseaseand to a much lesser degree in all types of liver disease. The widespread distribution and intensity of glial alteration and the relative absence of obvious parenchymal changes are, according to Adams and Foley, unique to cellular liver damage. Neurological synptoms probably can not be explained by glial changes, being due to some "subtle pathophysiologic changes of the neurones" with secondary changes as described above.

Some relationship has been postulated between hepatic coma and Hepato-Lenticular Degeneration, there being similarities in the organs involved. Generally speaking, the differences between the two diseases are more significant and pronounced, thus probably negating any possible correlation . (Different type of liver damage, lenticular invovement, Fleischer ring, different neurological manifestations and disturbance of Cu metabolism are seen in Wilson's disease (Adams and Foley-3).

Other workers have failed to describe the specific changes seen by Adams and Foley. Watson (4) described

areas of perivascular demyelinization and endothelial proliferation as being common findings in the brain of those dying in hepatic coma. Karl et al (2) described non-specific CNS changes....notably, edema, vascular congestion, perivascular cuffing and minute hemorrhages. These latter workers also reviewed pathological findings in the liver and kidneys. Liver sections showed marked variations microscopically, some displaying rather typical Laennec's cirrhosis. Occasional biliary proliferation with round-cell and fatty infiltration were described... also areas of centrilobular necrosis with marked cellular infiltration. Kidneys were often normal, although not infrequently showed some bile nephrosis, lower nephron nephrosis or intercapillary glomerulosclerosis.

In a study of acute liver insufficiency in chronic alcoholics, Philips and Davidson (5) reported a typical hepatic lesion complex of hyaline degeneration, liver cell necrosis and parenchymal disorganization. Although many of these cases reached comatose states, no true pathological findings related to liver coma per se were reported.

CLINICAL ASPECTS AND SYMPTOMATOLOGY

Although in its incipient and impending stages, hepatic coma presents a moderetly difficult diagnostic problem, recent studies and increased familiarity with the disease have lessened this problem. The generally accepted triad of symptoms on which the diagnosis is based are mental confusion, characteristic tremor and neurological changes and specific EEG changes in patients with known liver disease.

Adams and Foley (6), in their excellent review of neurological changes in hepatic coma, reported on 55 cases, dividing these into three basic groups. Group 1 was classified as "Fatal Hepatic Coma". Characteristically, patients in this group first displayed a mild restlessness or busy agitation for hours or days, followed by drowsiness, then stupor and finally deep coma. Clouding of consciousness, impairment of orientation and decrease of awareness were common signs in the stages preceding coma. Several types of tremors, reflex changes and rigidities were described. A plastic rigidity of elbows and wrists, resistance to passive movement and occasional true spasticity with eventual development of the grasping and sucking reflexes were seen in this group. Minor deep tendon reflex changes were common and the exstensor plantar response was present in half the patients of this series.

The so called "flapping tremor" is completely described by Adams and Foley (6). This tremor is considered quite characteristic by most authors and, along with the mental confusion and history of liver disease, is usually sufficient to make the diagnosis. As fully described, the tremor is absent at rest and on movement, being developed on active maintanance of posture (particularly of the upper extremities). The patient is instructed to hold his arms forward with the hands and fingers extended, sustaining this posture for a short while. Typically, rhythmical movements develop in a few seconds with occasional bursts of exacerbation....these movements consist of a side-to-side movement of the fingers, flexion and extension of the metacarpophalangeal joints, flexion-extension, radial-ulnar deviation and pronation-supination at the wrists with occasional abduction-adduction of the shoulder. Other disorders of the motor system can occur.....elevation of the leg and dorsiflexion of the foot causing episodes of flexion and extension of the ankle and knee (Adams and Foley-3).

Group 2 in Adams' and Foley's (6) classification is the "Recurrent Hepatic Stupor". This category includes patients who did not go into deep coma or death and is indistinguishable from less advanced stages of fatal coma. Motor and reflex changes are present....also marked tremors and extensor plantar responses are often

found, some individuals being normal between attacks. Group 3 was called the "Fixed Tremor State". These patients had recurrent episodes of stupor but gradually developed a persistant tremor. None of this group recovered completely normal mental function.

Walshe (7) describes the adoption of a position in which the legs are crossed and tightly drawn up to the abdomen. Also emphasized are pyramidal tract signs, occasional basal ganglion signs and unusual combinations of ankle clonus and plantor flexion. Walshe (7) considered the presence of nightmares to be of grave prognostic significance. Choreiform and athetoid movements, along with hallucinosis, nuchal rigidity, dilated pupils and occasional convulsions are described by Karl (2). Common findings in impending coma and liver disease, although of less diagnostic significance, are elevation of temperature, pulse and respiration, anorexia, ascites, hepatomegaly and edema (Karl-2, Murphy-8). Other findings found in cirrhosis,and thus occaionally present in coma, are collateral abdominal veins, spider nevi, liver palms, atrophic testes, fetor hepaticus, splenomegaly, gynecomastia, melana, hemorrhoids, abdominal pain, jaundice and diarrhea. The presence of fetor hepaticus is considered to be of poor prognostic significance by Watson (4)..... also of significance is a rapid decrease in liver size.

Secondary infection was commonly observed by many authors. Davidson (9) states that jaundice was much more common with the acute disease leading into coma than with the chronic disease. Watson (4) stressed the importance in realizing that fatal coma may occur with little or no jaundice.

Electroencephalograpic changes are almost invariably found in hepatic coma when one chooses to expend the time required in it's determination. Foley, Watson and Adams (10) studied EEG patterns in 26 patients with hepatic coma. They found that electrical signs of brain dysfunction in liver coma are "definite and distinctive with respect to distribution, wave form, frequency, bilateral synchronicity, episodic occurrence and association with normal cortical rhythms. A close correlation with the severity of the clinical disturbance was also described. The authors found an abnormal activity of about 2 per second frequency, a uniform frontal dysrhythmia occurring initially, followed by generalized abnormalities. The unique feature was said to be in the sharp contrast in early stages between bursts of slow waves and intervals of normal activity. These EEG changes, although characteristic, are nonethe-less non-specific and require a fairly typical clinical picture before substantiating a diagnosis of hepatic coma.

Differential diagnosis can be relatively simple yet quite important. Of greatest import is the avoidance of gall bladder surgery mistakenly in patients with severe liver disease. If a high degree of jaundice is present, the problem may be difficult. Other factors causing episodic stupor and possibly creating confusion in diagnosis are porphyria, uremia, hypoglycemia, acidosis, hypokalemia and hyponatremia. The latter four are particularly apt to occur in patients with severe liver damage, often complicating therapy as well as the diagnosis of true hepatic coma.

BIOCHEMICAL AND METABOLIC DISORDERS
(with associated laboratory findings)

It is in the realm of the clinical laboratory that the greatest advances in the understanding of hepatic coma have taken place. As stressed earlier, this syndrome occurring with liver failure is principally one of physiologic and metabolic derangement. It is for this reason that the following discussion is both lengthy and detailed, this author firmly believing that herein lies the way to a better understanding and appreciation of liver coma.

As the symptoms of hepatic coma are primarily based on central nervous system derangement, it might be thought that considerable information would be found in the brain's surrounding medium, the cerebrospinal fluid. Yet, studies on the cerebrospinal fluid during hepatic coma have been relatively sparse and non-illuminating. Further concentrated work on this body fluid, along with developments in technical procedures, may reveal much toward solving the problems of liver failure. Amatuzio (11) studied the spinal fluid in jaundiced patients with and without hepatic coma. With cirrhosis alone, no increase in protein was found, bilirubin being present in 8 of 10 patients. Bilirubin was found in the cerebrospinal fluid in 10 of 11 cases in coma, while the

spinal protein was elevated in each instance. Cell counts were normal in all cases. In earlier studies, Amatuzio (12) found elevated pyruvic acid levels in the spinal fluid of 8 of 12 patients in coma, hypoxia being experimentally excluded as the resposible mechanism. Adams and Foley (3), in their series of 25 cases, found neither pleocytosis nor abnormal protein elevation. Snell and Butt (13) performed spinal fluid studies in 2 patients, normal findings being found in both.

Abnormal electrolyte patterns are a common occurrence with liver coma and, more often than not, are important contributory factors in the demise of the patient. Carfagno et al (14), in a series of 11 patients, found 9 with significant hypokalemia, presumably on the basis of starvation and diarrhea. Other common findings in this series were hypocalcemia, acidosis and elevated pyruvic and lactic acid levels. Serum sodium and chloride levels are commonly depressed, often a result of over-enthusiastic therapy. Lowered Mg levels have also been noted by some authors. Abnormally low blood sugar levels, occasionally due to liver damage per se, may lead to coma and death.

NPN elevation and BUN elevation are extremely common findings as noted by both Karl (2) and Davidson (9). Various liver function tests show abnormalities as

expected with advanced liver disease. None are of value in determining the degree or probability of coma but serve to indicate the extent of liver damage present. Davidson (9) stresses the marked reduction of blood cholesterol esters with the onset of coma, the explanation not forthcoming. Carfagno (14) found the prothrombin time to be elevated in all of his 11 patients, there being no response to vitamine K. Generally, his series of cases showed normal thymol turbidity levels, two patients in overwhelming failure having negative cephalin-cholesterol floculation tests. Elevation of neutral fat and depression of phospholipids were found in a few cases. In Karl's (2) series, the thymol turbidity was abnormal in 65%, ceph-cholest. at 3-4 plus in 100%, BSP elevated in 94%, prothrombin time elevated in 94%, serum bilirubin elevated in 88%, serum albumin depressed in87%, serum globulin elevated in 85% and total cholesterols depressed in 69%.

No particularly valuable information has been gained in studies of erythrocytes or of bone marrow. Anemia has been a constant finding in most series, being either nomocytic, macrocytic or microcytic (Karl-2). Leucocytosis was found in 58%.

In the last few years, considerable work has been done on aminoacid and ammonia metabolism in the normal

and it's alteration and significance in the patient in liver coma. In particular, the role of glutamic acid and ammonia has received considerable impetus. Duncan (15), in discussing protein metabolism in the human, points out the role of both above mentioned substances in the normal individual, apparently their most significant role being in the production of urea. For purposes of clarification, it would be well to briefly review the method of formation of urea:

Ornithine plus CO_2 plus NH_3 ------→Citrulline

Citrulline plus NH_3 -----→Arginine

Arginine plus H_2O plus Arginase----→Urea plus Ornithine

The above diagram is classical but leaves out many subdivisions and contributing factors toward urea production. In the synthesis of citrulline, the aminoacid glutamate is found to act as an initial acceptor of the CO_2, giving rise to the substance carbamyl glutamic acid. The carbamyl group is then donated to ornithine and, with ammonia, citrulline is formed (the reaction being dependent on ATP). Thus is seen the apparent basic relationship between ammonia and glutamic acid, although other factors tend to thoroughly complicate the picture. Generally, clinical observers have thought of glutamic acid as binding with the "free ammonia" in the blood to form glutamine and eventually urea, the process probably taking place entirely within the liver.

Although the above stated reaction would not appear to take place directly, most authors apparently feel that the reaction at least gives a clear picture of a generally confusing topic. As pointed out by Seegmiller (16), " a close metabolic relation exists between ammonia metabolism and glutamine, these not being directly in the pathway to urea formation, but rather that glutamic acid offers a method for detoxifying and transporting ammonia". One would probably be wise to accept, for the time being, the role for glutamic acid as postulated by Seegmiller.

Other roles for glutamic acid have been postulated or rather convincingly proven. Among these is the role of glutamic acid in carbohydrate metabolism. Duncan (15) points to it's importance in the catalytic reactions of intermediary carbohydrate metabolism while Walshe (17) states that glutamic acid is deaminated to alph-keto-glutaric acid , which then enters the Krebs cycle. According to Walshe (17), the role of glutamic acid in the brain is based on three enzymatic reactions..... deamination, transamination and amidation....."all are part of the system for removing intracellular ammonia". Walshe (17) also found glutamic acid essential for AcH synthesis and cation transport in the brain, kidney etc.

As pointed out by Duncan (15),and worth mentioning for further attempts at clarification, the liver is

probably the chief site of deamination of the amino-acids, producing ammonia and keto acids (some workers feel that the wall of the GI tract and the kidney are the important sites of deamination rather than the liver). With removal of the liver, a decrease in blood urea and a marked rise in injected aminoacids (normally remains constant) is noted.....eventually, complete failure of urea formation occurs.

Thus one can objectively see the cause for increased ammonia levels in the blood and alterations in amino-acid types with severe liver disease, the clinical importance to be discussed shortly. Also, it is obvious why stress should be placed on the metabolism of glutamic acid, particularly if it is true that this substance is responsible for neutralizing and transporting blood ammonia. Although the exact metabolic picture is somewhat difficult to understand for the average clinician, and the entire story of metabolism in the human is far from complete, present knowledge has led to some important observations on altered ammonia and aminoacid metabolism in the abnormal state of hepatic coma....it's probable significance and it's response to therapy.

One of the big problems at present is the need for a more complete understanding of basic metabolism as we now know it.....quite frequently, workers in the

field of liver disease are either lax in their knowledge of metabolism or appear unable to present information in a complete and understandable manner. This would seem to lead to many therapeutic approaches in hepatic coma which are completely empirical.....although this in itself is not to be condemned, a plea should be made for better understanding and forthwith, more rational approaches to the problem of liver disease and hepatic coma.

As concerns the alteration in ammonia and aminoacid metabolism in hepatic coma, Walshe (7), in recent years, was one of the first to delve into the problem, He showed a rise in total aminoacids, as well as the presence of an occasional rare aminoacid in the urine and plasma of patients in liver coma. Walshe postulated that changes in aminoacid patterns were capable of producing varying neurological syndromes which would be potentially reversible and would not be associated with significant microscopic brain changes. The striking abnormality found by Walshe (7) was in the great excess of glutamine. Paper chromatography has shown profound disturbances of aminoacid metabolism in liver failure. Of most significance appears to be the great rise of glutamine concentration in the cerebrospinal fluid..... this may be due to an increase in cerebral ammonia

formation or to increased absorption of ammonia products from the gut and/or the failure of the liver to detoxify the ammonia passing thruugh. (Latter theory considered unlikely by Walshe-7).

Flock and Block (18) performed interesting studies on the changes in free aminoacids of the brain and muscle following total hepatectomy in dogs. They noted an accumulation of many free aminoacids of plasma after removal of the liver (if sufficient glucose given to prevent hypoglycemia). Glutamine, the most abundant aminoacid of the plasma, was noted to increase the most....particularly is this increasenoted in the brain while no significant changes in glutamic acid concentration were noted in the brain (a great decrease in glutamic acid was noted in muscle). The authors felt that altered brain metabolism was the cause of the high glutamine levels in the brain, mentioning the possibility that this aminoacid may be synthesized in the brain.

Seegmiller et al (16), in their discussion on ammonia and glutamine in hepatic coma, found that 15-25% of the total alpha-aminoacid of plasma was glutamine and felt that this may be increased in the abnormal state of liver coma. The above workers were unable to show any relation between clinical status and plasma glutamine levels..... they found a somewhat better correlation between plasma

ammonia and the clinical status, a direct quantitative relation lacking.

As regards blood ammonia levels, considerable studies and sharp controversies have raged over the last few years. When first introduced, blood ammonia studies were thought by many to be the important diagnostic feature in hepatic coma, elevated levels being directly correlated with the state of coma. As further work was done, the value of ammonia levels was questioned and it's exact role in the production of hepatic coma became somewhat more nebulous. Nonetheless, it cannot be denied that increased circulating ammonia appears to play a vital part in the production of hepatic coma and that it's understanding is of upmost importance as concerns modern thinking on the physiology of liver failure.

One of the most perplexing problems connected with ammonia metabolism is that dealing with the measurement of blood ammonia levels, a difficult procedure at best. The relationship between ammonia levels and the degree of coma will continue to be in doubt as long as there is doubt as to the accuracy of the procedure for measuring the concentration of the former. It must also be admitted that measurement of the latter is no better than the experience and judgement of the observer. Nelson (19) and Traeger (20) have adopted the ammonia analysis method of

Seligion and Hirahara. In this procedure, "free ammonia" is liberated from a sample of blood by contact with an alkalai, the ammonia being collected by diffusion and measured colorimetrically. Other workers have made use of the Conway microdiffusion method of ammonia analysis. The basic problem in measuring "free ammonia" levels is the uncertainty as to how much of the ammonia measured is actually circulating free in the blood and is not broken from a chemical bond during chemical determinations. For the present, and until more reliable methods are available, we must accept the above mentioned determinations as being fairly accurate and useful.

In general, studies have shown that significantly high levels of ammonia are present in the blood of patients with impending coma or coma of liver origin. Traeger (20) found that in patients with cirrhosis only, ammonia levels compared with the normal control while the highest levels were found in those with hepatic coma. Unfortunetly, the elevation in some patients did not exceed that found in others with cirrhosis only. Two patients showed serial ammonia increases while progressing from a clear state to coma, while oral ammonia chloride, when given to individuals with cirrhosis, caused a greater rise in ammonia levels than in normals. In Traeger's series, significantly elevated levels were

not found in five patients with hepatitis or four with uremia. In conclusion, Traeger, Gabuzda et al (20) found that ammonia metabolism was often derranged in cirrhosis; however, they were unable to sufficiently correlate ammonia levels with the state of consciousness and thus could not establish a causal relationship of ammonia to hepatic coma.

Schwartz et al (21), in their series of 22, noted an elevated blood ammonia level in patients with and without impending coma or coma. They also felt there was no precise correlation between ammonia concentration and the degree of consciousness. Mann, Bollman et al (22) found blood ammonia levels to be normally less than 2 micrograms. They noted an elevation in liver disease which was not exactly correlated with the degree of consciousness. These workers believed the ammonia elevations could be explained by circulatory considerations alone.....the partial by-passing of the cirrhotic liver by the portal system and the subsequent reduction of blood flow to this organ allowed for increased ammonia levels. (due to bacterial breakdown of nitrogenous substances in the gut.).

An interesting study on blood ammonia was made by Nelson and Seligson (19) on normal and shock states in dogs. This group noted a "constant rise in peripheral

blood ammonia in sustained hypotension". The renal and portal vein blood showed elevation while hepatic vein blood showed considerably lowered ammonia levels in the normal, an indication of the part played by the normal liver in the removal of ammonia from the body. In animals in hemorrhagic shock, this group found that blood from all vessels showed elevated ammonia levels, hepatic parenchym being unable to clear this substance adequatly during shock.

Within the last one to two years, considerable study and comment has been made on experimentally produced hepatic coma or syndromes unrecognizable from true liver coma. All of these studies have stressed the importance of ammonia or ammonia products in producing this comatose state. Phillips (23) was one of the first to show the untoward effects of ammonia containing compounds when given to advanced cirrhotics. Using such substances as ammonia potassium cation exchange resin, ammonia chloride, di-ammonium citrate, urea and increases of dietary protein in 9 patients, Phillips was able, in 5 cases, to provoke reactions clinically indistinguishable from impending hepatic coma. Numerous biochemical and electrolyte measurements revealed no consistent changes, although blood ammonia correlated best with the reactions observed.

Gabuzda et al (24) gave cation exchange resins to 12 patients with ascites (cirrhotics).....diuresis occurred in 10, but complications similar to hepatic coma also took place in those receiving resins containing ammonia. One case showed EEG changes characteristic of liver failure. The authors stressed the normality of biochemical findings other than the ammonia levels, although acidosis (to be distinguished by lack of tremor and altered mental status) did occasionally cause apathy and drowsiness. When hydrogen containing resins were used, these authors experienced no difficulties as related above.

Schwartz, Phillips, Gabuzda et al (25), in a recent article, showed that "individual tolerance to dietary protein exists in patients with cirrhosis and exceeding this tolerance may induce or aggrevate hepatic coma". One case, in their series of 3, showed signs of impending coma with a rise in dietary protein, while protein restriction resulted in a complete remission of signs and a reversal of the EEG pattern (these episodes were repeated on three occasions). The authors felt that the effect of excess protein was related to ammonia metabolism.....inability ti clear ammonia or effects similar to that seen with an Eck fistula.

McDermott and Adams (26,27), in two separate articles,

reported on the occurrence of episodic stupor in a human with an Eck fistula. The classical Eck fistula, as first evolved in the dog, involved a shunting of prtal blood directly into the inferior vena cava, by-passing the liver entirely. The patient followed by the above authors had the portal vein resected for carcinoma of the pancreas, a true Eck fistula being formed by the anastamoses of the superior mesentaric vein to the inferior vena cava. Previously, Eck fistula's had been formed in experimental amimals only, these having led to the work on the "meat intoxication" theory in dogs. The patient with the Eck fistula suffered a series of episodic stupors, characterized by confusion, coma, rigidity, and/or reflex grasping. The onset of these symptoms was always acute and ended, after several days, in complete recovery. High protein diet, ammonium chloride, and urea, when given to the subject, would produce neurological disorders similar to symptoms occurring with spontaneous onset. The authors felt that ammonia, which was always markedly elevated at the onset of stupor, was formed in the gut and not detoxified by the liver through which it could not pass.

PREVENTION AND THERAPY

Having thus concerned ourselves with the etiology, pathology, symptomatology and physiology of hepatic coma, we are now ready to delve into the problem which most concerns the public-at-large.....prevention and therapy of liver failure. Until recently, little in the way of therapy could be offered the patient in hepatic coma. With increased understanding and interest in the disease, physicians have adopted a new and challenging outlook toward a syndrome which still carries an extremely poor outlook.

For many years, therapy and prevention consisted mainly of dietary management and prayer.....these factors are still of upmost importance. As stated by Karl (2), Walshe (17) and Murphy (8), as well as other prolific writers on this subject, a nutritious diet, with generally high caloric, protein and vitamine supplements , is of great value. Tube feediggs or use of IV glucose, the latter in daily amounts of 1-3 liters of 5-20% dextrose, are commonly used. Glucose aannot be considered harmless....if given with complete disregard for electrolyte balance, one may be faced with the problem of a comatose patient, etiology being low potassium. Other electrolyte abnormalities commonly occur and are

deserving of careful and continuous check, the levels of sodium and the CO_2 combining power being of particular significance. As stated earlier, electrolyte derangements often simulate coma due to liver failure and may readily contribute to the demise of the patient. Excessive amounts of therapeutically administered electrolytes may often aggrevate the patients condition. The importance of the clinical laboratory, in the care and maintenance of the comatose patient, cannot be overemphasized.

The use of crude liver extracts and lipotropic agents, although probably never responsible for a patients recovery, are probably warrented as relatively harmless measures. Use of low salt regimen, along with diuretics to combat the ascites commonly seen, is rather standard practice and is probably indicated where findings warrent their use, again with a careful eye to electrolyte problems. In light of this, it is interesting to note Davidson's (9) comments on the apparent lack of water tolerance found in hepatic coma, suggesting an increased antidiuretic activity due either to "increased secretion or failure of inactivation of the hormone by the damaged liver". Because of the above findings, Davidson states that the use of hypertonic saline may occassionally be effective.

Parenteral proteins have been advocated by many authors (Murphy-8, Watson-4, Walshe-17) but Karl (2) has questioned the possible harmful effects of such substances as serum albumin and various amino acids. Of particular recent interest has been the studies with the Eck fistula in man (McDermott and Adams-26,27) as well as the meat intoxication syndrome observed in dogs with the same fistula (see previous comments). Because Because of these findings, the above authors have stressed the importance of a low protein diet. This was most recently pointed out, as previously mentioned, by Schwartz, Gabuzda et al (25) who showed dramatically the contribution played by dietary protein restriction in the relief of symptoms in a comatose patient. Although the importance of protein restriction as a measure of relief to the stuporous patient cannot be ignored and may warrent a trial, it should be used only in the more severe and unresponsive cases.....the building blocks of the body and its material for repair work are still the proteins brought to it from the outside.

Other therapy has been used in symptomatic measures.. .....sedatives are often required but should be used with upmost caution else they precipitate the comatose state. In this regard, Demerol and phenobarbital are probably somewhat safer to use. Correction of anemia is of no

small importance and paracentisis, when necessary, is valid treatment, repeated, small fluid withdrawels being best tolerated (Davidson-9). The importance of infection, localized or systemic, has been stressed by Murphy (8), sepsis often complicating liver failure. Vigorous antibiotic treatment is thus indicated.

Three other methods of therapy have become rather prominent in the literature in the last few years..... while offering hope and further stimulating interest, it would appear that neither ACTH, Cortisone, Aureomycin and/or glutamic acid in any combination are the final or ultimate answers to the problem of liver failure, if, indeed, their is one.

Farquhar, Stokes et al (28) noted a more severe degree of hepatic necrosis in the left lobe of the liver as compared to the right. Because the blood supply to the left lobe is principally from the large bowel, the authors felt that the severe necrosis was due to bacteria or their products from the colon. In their limited series, they noted dramatic response to the use of Aureomycin, postulating an antibacterial action on the gut or liver. Karl (2) also recommended the use of Aureomycin, both as an antibiotic and as a possible retarder of hepatic necrosis. Other authors (McDermott and Adams-26) have recommended the use of sulfa drugs as

a purely bacteriostatic drug causing subsequent reduction in blood ammonia levels. Finally, Davidson (9) would not recommend Aureomycin as a specific agent in hepatic coma because of the problem of severe staph diarrhea.

Aproximately two years ago, Walshe (17), in discussing the role of glutamic acid in the body and it's relationship with ammonia (see previous discussion), used the sodium salt of glutamic acid with benificial effects in 3 cases. Walshe postulated the mechanism as being of cerebral or hepatic function, the action of the salt being in binding ammonia or influencing favorably some aspect of the Krebs cycle. Riddell and McDermott (29), in a general discussion of hepatic coma, felt that glutamic acid may cause some improvement in the clinical picture. 23 grams of sodium glutamate was given to 8 patients in a series reported by Webster and Davidson (30), the patients being in impending coma, coma or impending coma induced by ammonia salts. These authors were unable to show any beneficial or preventative effects with the use of glutamate and found no constant changes in the ammonia blood levels.

The role of ACTH and/or cortisone has also received increased stress of late, whenever therapy in liver failure is discussed. In a complete series by Evans, Spring and Nelson (31), the effect of both hormones was

discussed in varying phases of liver disease. The two hormones were given to 6 comatose patients, all 6 dying without significant improvement, the authors admitting the possibility of initiating therapy too late. Their conclusion was that ACTH and cortisone, although of occasional value in certain forms of liver disease, are generally not indicated for routine use.

Ducci and Katz (32), in an earlier report, commented on the treatment of two patients with fulminant hepatitis leading to liver coma, These cases were treated with cortisone and aureomycin, spectacular response occurring in 48 hours. Recently, Alexander and Porter (33) reported on a deeply comatose patient in hepatic failure treated with 23 grams of Sodium glutamate ("Accent") IV, fluids and a total of 200 mg of ACTH. The result was gradual improvement and eventual release of the patient.

Loomis and Walsh (34) used steroid therapy in 18 cases with impending coma or coma, noting improvement clinically and laboratory-wise in 12 cases. High relapse rates were prevented by gradual reduction in the dosage of the steroids. In a symposium on liver coma moderated by Butt (1), the value of ACTH or cortisone was questioned, the moderator speculating that the steroids may cause an actual elevation of blood ammonia.

SUMMARY

Hepatic coma is a syndrome of metabolic derangement occurring with severe hepatic dysfunction, following either a chronic degenerative process or complicating an exceptionally acute liver inflammation. Numerous factors may initiate the comatose state, notably starvation, recent alcoholic debauch and generalized worsening of the liver condition. Iatrogenic factors are all to common in precipitating liver coma.

Neuropathological studies have revealed little in the understanding of the subtle biophysiologic changes present in hepatic coma. Recent studies have shown a rather non-specific glial change in the Central Nervous System.....increase and enlargement of protoplasmic astrocytes. Other brain changes, as seen under the microscope, are highly non-specific as are changes in all other organ systems of the body. The liver shows changes typical of either acute or chronic liver disease.

The symptom complex, along with the history of liver disease, is the only definitive method of diagnosing hepatic coma. Mental confusion and restlessness are the symptoms observed initially in hepatic failure, the comatose state finally intervening. Development of the typical "flapping tremor" of the outstreched arms is characteristic and usually establishes the diagnosis.

Numerous other non-specific reflex and neurological changes may be observed, no particular pattern or order of involvement being observed. EEG changes are characteristic in coma of liver failure, usually not being necessary to establish the diagnosis in clear cut cases and of little value in the more questionable circumstances. Physical findings common to cirrhosis are, as would be expected, often present in liver coma. As no laboratory tests are, as yet, of definite value in all cases of hepatic coma, one must still rely on the acumen of the physician for the final diagnosis.

Being primarily a metabolic abnormality, hepatic coma may be more readily studied and understood in the clinical laboratory. Abnormal electrolyte patterns, whether due to neglect or faulty therapy, are common findings in this disease process. Liver function tests generally show severe liver damage but present no specific findings in hepatic coma. Cerebrospinal fluid studies have been singularly unenlightening, although alteration in protein content do appear. Aminoacid changes, particularly as concerns glutamine, have been noted by many authors, the elevation of these substances being particularly noteworthy. Although considerable work has been done, no correlation has been shown between aminoacid levels (glutamine) and the state of coma.

Blood ammonia levels have been of considerable interest in the last few years, most workers noting a marked increase in hepatic coma. Again, no direct correlation between ammonia concentration and the state of coma has been convincingly shown, although work along this line holds much promise. It would appear that elevated ammonia levels, due to failure of detoxification in the damaged liver, are an important factor in the production of the neurological syndrome and eventual death of the patient in hepatic failure. Along this line have been the numerous studies on the effects of ammonia containing compounds and high protein diets in precipitating liver coma, or syndromes resembling this disease, in patients with severe hepatic derangement.

Therapy in hepatic coma has made considerable progress over the last decade; nevertheless, preventive measures are of greatest importance, the prognosis in liver coma being uniformily poor. Porper dietary regimen and adequate supplements are of great value.....the use of a low protien diet should be used only in highly selected cases. Attention to the correction of any electrolyte imbalance is particularly important and necessary. Glutamic acid, in spite of initial favorable reports, appears to offer little aid. Use of antibiotics, particularly Aureomycin, may be of value but occasionally

creates difficult complications. ACTH and cortisone seem to have a favorable effect, both subjectively and objectively, on patients with severe liver damage. Although opinion is far from unanimous, steroid therapy appears to be useful in the more severe cases of liver failure.

This author is particularly grateful to Dr. George Loomis for his unquestionable aid in the initiation and compilation of data necessary for writing this review.

CONCLUSION

This review has concerned itself with a complete study and evaluation of a syndrome occasionally occurring in patients with marked liver damage....hepatic coma. A brief resume' of important etiologic factors was given. Following this, was a review of the neuropathological findings in hepatic coma, emphasis being placed on the limited and non-specific findings present in the CNS in this syndrome. A complete description of the clinical findings and symptomatology was presented, particular reference being made to the mental confusion, and restlessnes and typical flapping tremor present prior to coma. A discussion of the numerous metabolic derangements present in liver failure followed, considerable stress being placed on the role of aminoacids and ammonia in this disease, along with the effects produced by ammonia-containing substances. Finally, a general picture of the trends in therapy was reviewed, supportive treatment and steroid being of primary importance at the present time.

(appendix III)

BIBLIOGRAPHY

1. Butt, H.--moderator, panel discussion: The Clinical and Biochemical Features of Hepatic Insufficiency. Gastroenterology- 25:471 (Dec.) 1953.

2. Karl, M.M.,; Howell, R.A.; Hutchinson, J.H., and Catanzaro, F.J.: Liver Coma, with Particular Reference to Management. Arch. of Int. Med. 91:159 1953.

3. Adams, R.D. and Foley, J.M.: Metabolic and Toxic Diseases of the Nervous System: The Neurological Disorders Associated with Liver Disease. Res. Pub. of Ass. for Res. in Nerv. and Ment. Diseas. 32--1953.

4. Watson, C.J.: The Prognosis and Treatment of Hepatic Insufficiency. Ann. of Int. Med. 31:3-405 (Sept.) 1949.

5. Phillips, G.B., and Davidson, C.S.: Acute Hepatic Insufficiency of the Chronic Alcoholic. Arch. of Int. Med. 94:585 1954.

6. Adams, R.D. and Foley, J.M.: Neurological Changes in the More Common Types of Severe Liver Disease. Trans. of the Amer. Neur. Ass. 74:217 1949.

7. Walshe, J.M.: Observations on the Symptomatology and Pathogenesis of Hepatic Coma. Quart. Jour. of Med. 20:421 (Oct.) 1951.

8. Murphy, T.L.; Chalmers, T.; Eckhardt, R.E.; and Davidson, C.S.: Hepatic Coma. N. Eng. J. of Med. 289:605 1948.

9. Davidson, C.S.: Cirrhosis of the Liver. Am. J. of Med. 16:863 1954.

10. Foley, J.M.; Watson, C.W.; and Adams, R.D. Significance of the Electroencephalographic Changes in Hepatic Coma. Trans. of the Amer. Neur. Ass. 75:161 1954.

11. Amatuzio, D.S.; Weber, L.J. and Nesbitt, S. Bilirubin and Protein in the Cerebrospinal Fluid of Jaundide Patients with Severe Liver Disease with and without Hepatic Coma. J. of Lab. and Clin. Med. 41:615 1953.

12. Amatuzio, D.S. and Nesbitt, S.; A Study of Pyruvic Acid in the Blood and Spinal Fluid of Patients with Liver Disease with and without Hepatic Coma. J. of Clin. Invest. 29:1486 1950.

13. Snell, A. and Butt, H.R.: Hepatic Coma: Observations Bearing on It's Nature and Treatment. Trans. of the Ass. of Amer. Phys. LVI:321 1941.

14. Carfagno, S.C.; De Horatius, R.F.; Thompson, C.M. and Schwartz, H.P.: Hepatic Coma. N. Eng. J. of Med. 246:303 (Aug) 1954.

15. Duncan, G.G.: Diseases of Metabolism---Protein Metabolism. 3d edition Philad. W.B. Saunders, 1952. P. 107-152.

16. Seegmiller, J.E.; Schwartz, R.; and Davidson, C.S.: Plasma "Ammonia" and Glutamine Contents in Patients with Hepatic Coma. J. of Clin. Invest. 33:7-984 (July) 1954.

17. Walshe, J.M.: The Effect of Glutamic Acid on the Coma of Hepatic Failure. Lancet 1:1075 (May) 1953.

18. Flock, E.V.; Block, M.A.; Grindlay, J.H.; Mann, F.C. and Bollman, J.L.: Changes in Free Amino Acids of Brain and Muscle After Total Hepatectomy. J. of Biol. Chem. 200:529 1953.

19. Nelson, R.M. and Seligson, D.: Studies on Blood Ammonia in Normal and Shock States. Surgery 34:1 1953.

20. Traeger, H.S.; Gabuzda, G.J.; Ballou, A.N.; and Davidson, C.S.: Blood "Ammonia" Concentration in Liver Disease and Liver Coma. Metab. III p.99 (March) 1954.

21. Schwartz, R.; Phillips, G.B.; Gabuzda, G.J. and Davidson, C.S.: Blood Ammonia and Electrolytes in Hepatic Coma. J. of Lab. and Clin. Med. 42:499 (Oct) 1953.

22. Mann, J.D.; Bollman, J.L.; Huizenga, K.A.; Farrar, T. and Grindlay, J.H.: Blood Ammonia; Experimental and Clinical Study in Abnormalities of the Liver and Portal Circulation. Gastroent. 27:399 (Oct.) 1954.

23. Phillips, G.B.; Schwartz, R.; Gabuzda, G.J. and Davidson, C.S.: The Syndrome of Impending Hepatic Coma in Patients with Cirrhosis of the Liver Given Certain Nitrogenous Substances. N. Eng. J. of Med. 247:239 1952.

24. Gabuzda, G.J.; Phillips, G.B. and Davidson, C.S.: Reversible Toxic Manifestations in Patients with Cirrhosis of the Liver Given Cation-Exchange Resins. N.Eng. J. of Med. 246:124 (Jan.) 1952.

25. Schwartz, R.; Phillips, G.B.; Seegmiller, J.E.; Gabuzda, G.J. and Davidson, C.S.: Dietary Protein in the Genesis of Hepatic Coma. N. Eng. J. of Med. 251:685 (Oct) 1954.

26. McDermott, W. and Adams, R.O.: Eck -Fistula: A Cause of Episodic Stupor in Humans. J. of Clin. Invest. 32:587 (June) 1953.

27. McDermott, W. and Adams, R.O.: Episodic Stupor Associated with an Eck Fistula in the Human with Particular Reference to the Metabolism of Ammonia. J. of Clin. Invest. 33:1 (Jan.) 1954.

28. Farquhar, J.D.; Stokes, J.S.; Whitlock, C.M.; Bluembe, L.W. and Gambescia, J.M.: Studies on the Use of Aureomycin in Hepatic Disease---- Note on Aureomycin Therapy in Hepatic Coma. Amer. J. of Med. Sciences. 220:166 1950.

29. Riddell, A.G. and McDermott, W.: Hepatic Coma. Lancet. p.1263 (June) 1954.

30. Webster, L.T. jr. and Davidson, C.S.: Hepatic Coma: Effect of Sodium Glutamate. J. of Clin. Invest. 33:971 1954.

31. Evans, A.S.; Spring, H. and Nelson, R.S.: Adrenal Hormone Therapy in Viral Hepatitis. I-The Effect of ACTH in the Acute Disease. II-The Effect of Cortisone in the Acute Disease. III-The Effect of ACTH and Cortisone in Severe and Fulminant Cases. Ann. of Int. Med. 38:1115 (June) 1953.

32. Ducci, H. and Katz, R.: Cortisone, ACTH and Antibiotics in Fulminant Hepatitis. Gastroent. 21:357 1952.

33. Alexander, J.W. and Porter, C.E.: The Treatment of a Patient in Hepatic Coma with Intravenous Sodium Glutamate and ACTH. Gastroent. 26:926 (June) 1954.

34. Loomis, G.L. and Walsh, J.R.: Adrenocortical Therapy in Hepatic Insufficiency. Unpublished data.