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Brain Dysfunction in Metabolic Disorders

Edited by Fred Plum

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Volume 53

Editor:

Fred Plum, M.D.
Professor of Neurology
Cornell University Medical College
and
Neurologist-in-Chief
The New York Hospital

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Preface

In recent years, neurologists and psychiatrists have increasingly concerned themselves with the biochemical effects of systemic diseases on the brain. Much of this concern stems from mere clinical need—in most hospitals almost as many patients have neurological and behavioral symptoms resulting from systemic disease as from primary neurologic or psychiatric illnesses. Another factor has been that in many systemic diseases, uremia and liver disease being prominent examples, a major goal of treatment has been to keep patients free of neurological signs and symptoms. Indeed, some systemic illnesses and conditions are dangerous only when they induce neurological abnormalities. Finally, an understanding of some of the specific biochemical mechanisms by which systemic metabolic changes affect the nervous system has helped to explain many of the intrinsic chemical processes and susceptibilities of the brain and its outcroppings. All these considerations stimulated the Association to hold the meeting upon which this volume is based at this particular time.

The Association first considered Toxic and Metabolic Diseases of the Nervous System at its annual meeting 21 years ago, and we stand in this volume on the shoulders of those who made so many important contributions at that meeting and thereby stimulated much of the work reported at this one. For organizing the present meeting it is my pleasure to acknowledge the considerable effort and thought applied by the Program Committee, the Officers and Trustees of the Association and the members of the Commission. Miss Harriette Bailie deserves particular thanks for her ever-skillful and experienced guidance which makes putting on the annual meeting an altogether pleasant task. Finally, we especially celebrate the new collaboration between the Association and Raven Press. The energetic and effective efforts of this distinguished publisher will henceforth enable the Proceedings to appear within the year following each meeting.

Fred Plum, M.D.

Participants

H. L. Bradlow
Rockefeller University
and
Department of Medicine
Cornell University Medical College
New York, New York 10021

J. B. Cavanagh
M.R.C. Research Group in Applied Neurobiology
Institute of Neurology
London, England

Ivan Diamond
Departments of Neurology and Pediatrics
University of California
School of Medicine
San Francisco, California 94143

Thomas E. Duffy
Department of Neurology
Cornell University Medical College
New York, New York 10021

V. Fencl
Departments of Physiology and Biochemistry
Harvard Medical School
Boston, Massachusetts 02115

James A. Ferrendelli
Departments of Neurology and Pharmacology
Washington University School of Medicine
St. Louis, Missouri 63110

Josef E. Fischer
Department of Surgery
Massachusetts General Hospital
and Harvard Medical School
Boston, Massachusetts 02114

Robert A. Fishman
Department of Neurology
University of California School of Medicine
San Francisco, California 94143

Gilbert H. Glaser
Department of Neurology
Yale University School of Medicine
New Haven, Connecticut 06510

Gary W. Goldstein
Departments of Neurology and Pediatrics
University of California School of Medicine
San Francisco, California 94143

S. Granick
Rockefeller University
and
Department of Medicine
Cornell University Medical College
New York, New York 10021

David C. Howse
Department of Neurology
Cornell University Medical College
New York, New York 10021

Halldor Jóhannsson
Brain Research Laboratory
E-Blocket
University Hospital of Lund
Lund, Sweden

A. Kappas
Rockefeller University
and
Department of Medicine
Cornell University Medical College
New York, New York 10021

M. L. Karnovsky
Departments of Physiology
and Biochemistry
Harvard Medical School
Boston, Massachusetts 02115

G. Koski
Departments of Physiology
and Biochemistry
Harvard Medical School
Boston, Massachusetts 02115

Bengt Ljunggren
Brain Research Laboratory
E-Blocket
University Hospital of Lund
Lund, Sweden

Steven Matthysse
Department of Psychiatry
Harvard Medical School
Boston, Massachusetts 02115

Alton Meister
Department of Biochemistry
Cornell University Medical College
New York, New York 10021

Urs A. Meyer
Department of Medicine
University of California
San Francisco, California 94122

Karin Norberg
Brain Research Laboratory
E-Blocket
University Hospital of Lund
Lund, Sweden

J. R. Pappenheimer
Departments of Physiology and Biochemistry
Harvard Medical School
Boston, Massachusetts 02115

Fred Plum
Department of Neurology
Cornell University Medical College
New York, New York 10021

Martin Reivich
Cerebrovascular Research Center
Department of Neurology
University of Pennsylvania
Philadelphia, Pennsylvania 19104

Leon E. Rosenberg
Department of Human Genetics
Yale University School of Medicine
New Haven, Connecticut 06510

Edward J. Sachar
Department of Psychiatry
Albert Einstein College of Medicine
Bronx, New York 10411

S. Sassa
Rockefeller University and
Department of Medicine
Cornell University Medical College
New York, New York 10021

Rudi Schmid
Department of Medicine
University of California
San Francisco, California 94122

Bo K. Siesjö
Brain Research Laboratory
E-Blocket
University Hospital of Lund
Lund, Sweden

Fernando Vergara
Department of Neurology
Cornell University Medical College
New York, New York 10021

Maurice Victor
Department of Neurology
Case Western Reserve University School of Medicine
Cleveland, Ohio 44106

Myron Winick
Institute of Human Nutrition
Columbia University
College of Physicians and Surgeons
New York, New York 10032

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Neurologic Changes in Liver Disease

Maurice Victor

Case Western Reserve University School of Medicine, Cleveland, Ohio 44106

The occurrence of cerebral symptoms in the course of liver disease—or hepatic encephalopathy—represents a common and serious clinical problem. Relatively effective measures are available for the treatment of hepatic encephalopathy as well as for the familial form of hepatolenticular degeneration (Wilson's disease), but effectiveness of treatment depends to a large extent on early recognition of the clinical state and an understanding of its pathogenesis—so these become matters of considerable practical importance. It should be pointed out that many of the clinical and pathologic features that characterize hepatic encephalopathy are not specific to this particular form of metabolic disease; what we learn about its mechanisms may therefore be helpful in understanding other metabolic disorders of the nervous system as well.

Our understanding of liver-brain relationships has been derived mainly from the study of three clinical syndromes: (1) the relatively acute neurologic disorder that complicates (or terminates) liver failure, i.e., hepatic coma; (2) the chronic familial type of hepatocerebral degeneration described by Westphal (1883), Strümpell (1897, 1898), and Wilson (1912); and (3) the acquired (non-Wilsonian) type of chronic hepatocerebral degeneration. Each of these disorders has been studied for many years but only recently have their relationships come to be appreciated.

HEPATIC COMA

That liver disease may be associated with a derangement of mental function has been known for a long time, perhaps since antiquity. Allusions to this association are apparently to be found in the writings of Hippocrates (460–370 B.C.), Galen (A.D. 131–200), Celsus (A.D. 30), and Shakespeare, but these are hardly worth repeating. A number of medical writings of the seventeenth, eighteenth, and nineteenth centuries contain descriptions of a clinical state in which jaundice was associated with delirium, seizures, and terminal coma (see reviews of Walshe, 1951; Summerskill, Davidson, Sherlock, and Steiner, 1956; Sherlock, 1958). The first detailed account of what we recognize today as hepatic coma is usually credited to Frerichs

(1861), who described confusion, seizures, and delirium, followed by progressive stupor and coma in patients with "acute yellow atrophy." Leyden in 1866 used the word cholaemia (literally, bile in the blood) to describe the clinical state in which jaundice was associated with a derangement of mental function. This term remained in general use until quite recently to designate any ill-defined disorder of behavior and consciousness associated with severe liver disease, despite the convincing demonstration by Frerichs (1861)—5 years before Leyden coined the term cholaemia—that the intravenous injection of bile in dogs did not give rise to disturbances of nervous function.

It should be pointed out that the cerebral abnormalities noted by Frerichs and other authors of his period to complicate liver disease were associated with liver disease of a particular type, i.e., "acute yellow atrophy." Frerichs (1861), in his chapter on cirrhosis of the liver, was equally emphatic that in patients with *chronic liver disease* the nervous system remained undisturbed. Such patients, he stated, endured their suffering in a gloomy and collected frame of mind and frequently retained consciousness until the very end of their illness. Budd (1846), in his monograph "On Diseases of the Liver" was also of the opinion that in chronic liver disease "the intellect and senses are usually free from disorder to the last."

Among the first to appreciate that a characteristic disturbance of mental function may complicate chronic liver disease was William Osler. He wrote, in the 1892 edition of his textbook, that "at any stage of atrophic cirrhosis the patient may develop cerebral symptoms, either a noisy joyous delirium, or stupor, coma, or even convulsions. The condition is not infrequently mistaken for uraemia. The symptoms may develop without jaundice and cannot be attributed to cholaemia, and they may come on in hospital when the patient has not had alcohol for weeks."

Except for the repetition of these observations in succeeding editions of Osler's textbook, the medical literature was remarkably silent on this matter until the 1940s, when a series of publications drew attention to hepatic coma as a complication of chronic liver disease, particularly of alcoholic cirrhosis (Snell and Butt, 1941; Greene, 1941; Murphy, Chalmers, Eckhardt, and Davidson, 1948; Gaustad, 1949). It was during this decade that the term hepatic coma came into common use. These authors made it clear that hepatic coma was not invariably a terminal occurrence but that it could be a transient event in the course of chronic liver disease and that it could recur. It is also apparent from these writings that neurologic abnormalities, other than those of mentation and consciousness, were not considered to be an integral part of the syndrome of hepatic coma—despite the fact that such abnormalities had been noted sporadically to complicate liver disease (see review of Walshe, 1951). In fact, as late as 1948 it was stated by the most authoritative hepatologists that apart from loss of consciousness there was no physical sign or biochemical estimation that made it possible to dis-

tinguish the comatose from the noncomatose patient with liver disease (Murphy et al., 1948).

This is where the matter rested as little as 25 years ago. Disordered nitrogen metabolism had already been studied a number of times, but these studies were concerned primarily with the urea-forming ability of the normal and diseased liver and were not related specifically to the clinical problem of hepatic coma. In 1877 Eck had devised a means of diverting blood from the portal vein into the inferior vena cava through a surgically constructed fistula. A particularly interesting phenomenon in dogs subjected to this procedure was "meat intoxication," a neurologic disorder that consisted of stupor, ataxia, convulsions, and finally coma, and which followed the ingestion of meat or occurred spontaneously. It was suggested by Mathews in 1922 that ammonia might be a causative factor in this syndrome. Later, Monguio and Krause (1934) related meat intoxication in the Eck-fistula dog to intestinal ammonia production and to the blood ammonia content. On the basis of their studies in dogs, Monguio and Krause recommended that "in cases of injury to the parenchyma of the liver, preferably a diet poor in protein and rich in carbohydrates should be prescribed."

A number of early investigators also found elevations of blood ammonia in patients with cirrhosis of the liver (Burchi, 1926; Van Caulaert and Deviller, 1932; Fuld, 1933; Kirk, 1936), and one of them (Fuld, 1933) noted that blood ammonia levels in cirrhotics returned to normal levels when their diet was poor in protein. Mainly these investigations consisted of feeding patients large amounts of ammonium salts and measuring the rise in blood ammonia concentrations. An incidental finding, noted by Van Caulaert, Deviller, and Halff (1932) and by Gaustad (1949) was the occasional occurrence of drowsiness, delirium, convulsions, and coma of short duration following ingestion of ammonium salts, but these observations were not pursued.

The modern concept of hepatic coma had its origin in the classic studies of Adams and Foley (1949*a*, *b*, 1953), Foley, Watson, and Adams (1950), and Gabuzda, Phillips, and Davidson (1952) at the Boston City Hospital. At the 1952 meeting of the Association for Research in Nervous and Mental Disease, Adams and Foley gave an account of their clinical and pathologic investigations into the neurologic disorder associated with liver disease. The clinical syndrome they delineated consisted essentially of a derangement of consciousness, presenting first as mental confusion with increased or decreased psychomotor activity, followed by progressive drowsiness, stupor, and coma. The confusional state, before coma intervened, was frequently combined with a characteristic intermittency of sustained muscle contraction, imparting an irregular "flapping" movement to the outstretched hands —a phenomenon to which the term asterixis was applied. The electroencephalogram (EEG) proved to be a sensitive and reliable indicator of impending coma, becoming abnormal during the earliest phases of the disordered mental state. The usual EEG abnormality consisted of paroxysms of bi-

laterally synchronous slow waves, in the delta range, which at first were interspersed with alpha activity and later, as the coma deepened, displaced all normal activity. A small number of patients showed only random high voltage asynchronous slow waves. The variable occurrence of a fluctuating rigidity of the trunk and limbs, grimacing, suck and grasp reflexes, exaggeration or asymmetry of tendon reflexes, Babinski signs, and focal or generalized seizures rounded out the clinical picture. This state, which complicated all varieties of liver disease, evolved over a period of days to weeks and often terminated fatally; or, after reaching a certain stage, the symptoms sometimes regressed completely.

The striking neuropathologic changes in these patients was a diffuse increase in the number and size of the protoplasmic astrocytes in the deep layers of the cerebral cortex, lenticular nuclei, thalamus, substantia nigra, and red, dentate, and pontine nuclei, with little or no visible alteration in the nerve cells or other parenchymal elements. This astrocytic change was described originally by von Hösslin and Alzheimer (1912) in a case of Westphal-Strümpell pseudosclerosis, and was observed subsequently with other varieties of liver disease (Insabato, 1924; Pollak, 1927; Scherer, 1933; Stadler, 1939), but not until Adams and Foley described their findings was the astrocytic hyperplasia related so explicitly to the syndrome of hepatic coma. They found that the astrocytic alterations occurred to some degree in all patients who died of progressive liver failure and that the degree of this glial abnormality was roughly parallel to the intensity and duration of the neurologic disorder. They also pointed out that the clinical and EEG features, as well as the protoplasmic hyperplasia, though highly characteristic of hepatic coma, were not specific features of this metabolic disorder. Nevertheless, taken together in a setting of liver failure these manifestations constituted a distinctive clinicopathologic entity.

The description by Adams and Foley of the syndrome of hepatic coma in all its stages provided a tangible device for investigating the mechanisms of the disease and consequently for its treatment. If nothing else, the timing of their studies was fortuitous, for while the clinical features of hepatic coma were being elaborated, Gabuzda and his colleagues (1952) in the Thorndike Memorial Laboratory at Boston City Hospital were investigating the diuretic properties of ammonium cation-exchange resins in patients with hepatic cirrhosis. The oral administration of these resins, which bind sodium and liberate ammonium, did indeed induce a diuresis in their cirrhotic patients, but it consistently induced a group of neurologic and EEG abnormalities as well, which Gabuzda and co-workers were able to recognize as the early manifestations of hepatic coma ("impending" hepatic coma). They showed further that the neurologic disorder precipitated by the ammonium resins was not related to alterations of the serum sodium or potassium concentrations or to the degree of acidosis. Since ammonium was released by the resins and since the metabolism of this substance involves the production

of urea by the liver, they proposed that the cirrhotic patients were not able adequately to remove the ammonium from the blood and that the neurologic abnormalities in these patients might be due to ammonium intoxication (Gabuzda et al., 1952).

In a series of subsequent studies the same investigators showed that a syndrome identical to hepatic coma could be provoked in cirrhotic patients by administering ammonium chloride, diammonium citrate, urea, or dietary protein; withdrawal of these agents or restriction of protein intake resulted in remission of the signs of hepatic coma and reversal of the EEG pattern to normal (Phillips, Schwartz, Gabuzda, and Davidson, 1952; Schwartz, Phillips, Seegmiller, Gabuzda, and Davidson, 1954).

Shortly thereafter, McDermott and Adams (1954) reported their observations of a patient in whom the superior mesenteric vein was joined to the side of the inferior vena cava, a procedure necessitated by the extensive resection of a carcinoma of the head of the pancreas. The liver at the time of the operation was free of disease, so that a true Eck fistula had been constructed, perhaps for the first time in man. Recurrent episodes of stupor, corresponding closely with elevations of blood ammonium, were precipitated in this patient by administering the same nitrogenous substances that had produced hepatic coma in patients with cirrhosis. Thus it was established that an abnormality of nitrogen metabolism, and more specifically an elevated blood ammonium level, was a fundamental factor in the genesis of hepatic coma; moreover, many of the earlier observations, which until this time had been largely neglected, could now be embodied in a coherent concept of the pathogenesis of hepatic coma.

During the decade that followed, these observations were repeatedly confirmed and amplified. In particular, the definition of the clinical state was broadened considerably. In a series of reports beginning in 1954 Sherlock and her group at the Postgraduate Medical School in London gave a detailed description of a chronic but nevertheless reversible mental disturbance in patients with chronic liver disease. This abnormal mental state, often associated with other neurologic symptoms, was protracted over a period of months or years. In these patients an extensive portal-systemic collateral circulation could be demonstrated by trans-splenic portal venography (hence their term portal-systemic encephalopathy), and an association was established between the mental disturbance and an intolerance to dietary protein and raised blood ammonium levels (Sherlock, Summerskill, White, and Phear, 1954; White, Phear, Summerskill, and Sherlock, 1955; Summerskill et al., 1956).

A diffuse increase in the number and size of protoplasmic astrocytes, now generally referred to as Alzheimer type II astrocytes, has proved to be a consistent neuropathologic change in patients with advanced liver disease and with hyperammonemia from other causes (Bruton, Corsellis, and Russell, 1970). The significance of the astrocytic hyperplasia is only poorly

understood. Recent experiments in rats and dogs with portacaval anastomoses (Cavanagh and Kyu, 1971; Norenberg and Lapham, 1974; Norenberg, Lapham, Nichols, and May, 1974) and in monkeys with sustained hyperammonemia in the absence of liver disease or portal-systemic shunts (Cole, Rutherford, and Smith, 1972) are beginning to shed light on the meaning of this astrocytic change.

During the past two decades the pathogenesis of hepatic coma has been the subject of intense investigation—and not a little controversy. The space allotted to these introductory remarks permits only some cursory comments concerning this subject, and the interested reader is referred to a number of authoritative reviews of hepatic coma in which the pathogenesis of the disorder and, particularly, the role of ammonium are considered in great detail (Gabuzda, 1962; Schenker, McCandless, Brophy, and Lewis, 1967; Gabuzda, 1967; Walker and Schenker, 1970; Breen and Schenker, 1972). It is now generally accepted that hepatic coma is associated with an increased concentration of ammonium or an ammonium-like substance in the blood. Despite the gaps in our understanding it, it is an awareness of this relationship that has provided the few effective means to treat hepatic coma: restriction of dietary protein; mechanical cleansing of the bowel; oral administration of neomycin, which eliminates urease-producing organisms from the bowel; surgical exclusion of the colon; and in recent years the use of lactulose, an inert sugar that effectively acidifies the colonic contents (Elkington, Floch, and Conn, 1969; Rorsman and Sulg, 1970). Conversely, the salutory therapeutic effects of these measures, the common attribute of which is the lowering of blood ammonium, lends strong support to the theory of "ammonium intoxication."

This brief statement stressing the central role of disordered ammonium metabolism in the genesis of hepatic coma, is not intended to deny the complexity of the subject or the importance of other factors in precipitating the clinical syndrome. It is intended to support the view that until now no "toxic" compound has been more positively incriminated in the genesis of hepatic coma than ammonium (Gabuzda, 1967); and if the "ammonium theory" does not explain all aspects of hepatic coma, it explains more of them and explains them better than any alternate theory proposed to date.

CHRONIC HEPATIC ENCEPHALOPATHY

Although the term hepatic coma is deeply entrenched in medical parlance, *hepatic encephalopathy*, qualified by the adjective acute or chronic, seems preferable. In some patients the evolution of symptoms stops short of coma; in others, the symptoms are neither evanescent nor terminal (as the designation hepatic coma has come to imply) but chronic in nature. Reference has already been made to a chronic form of hepatic encephalopathy described by Sherlock and her colleagues (Sherlock et al., 1954; White et al., 1955; Summerskill et al., 1956) in which a disorder of mood, personality, and

intellect extends over a period of months or even years. Despite their chronicity, the neuropsychiatric symptoms described by these authors fluctuate widely in severity or are intermittent in nature; they are essentially reversible if proper therapeutic measures are instituted. For this reason, this chronic syndrome accords more closely with hepatic coma in its many variations than with the chronic hepatocerebral syndrome described below.

The relatively fixed and irreversible cases of chronic hepatocerebral disease fall into one of two categories. The first includes classic Wilson's disease (hepatolenticular degeneration) and Westphal-Strümpell pseudosclerosis. These two disorders are now regarded as identical and are characterized by a *familial* occurrence, Kayser-Fleischer corneal rings, and abnormalities of copper metabolism. The second is an *acquired* form of hepatocerebral disease, in which these three characteristics are lacking. The latter form bears a more readily discernible relationship to hepatic coma than the former.

Acquired (Non-Wilsonian) Chronic Hepatocerebral Degeneration

Patients who survive an episode of hepatic coma are occasionally left with residual neurologic abnormalities, such as tremor of the head or arms, asterixis, grimacing, choreatic twitching of the limbs, dysarthria, ataxia of gait, or impairment of intellectual function, and these symptoms may worsen with repeated episodes of coma. In other patients with chronic liver disease, permanent neurologic abnormalities may become manifest in the absence of discrete episodes of hepatic coma. In either event, patients thus afflicted deteriorate neurologically over a period of years. Examination of the brain of such patients discloses foci of destruction of nerve cells and other parenchymal elements in addition to a widespread transformation of astrocytes, changes that are indistinguishable from those of Wilson's disease.

Probably the first to describe the acquired type of hepatocerebral degeneration was van Woerkom (1914–1915), whose report appeared only 2 years after Wilson's classic description of the familial form. Since then, there have been sporadic reports of the acquired disease. A full account of these as well as of our own extensive experience with this disorder appears elsewhere (Victor, Adams, and Cole, 1965) and is only summarized here.

The core of the clinical syndrome consists of dementia of varying degree, a rather characteristic dysarthria, ataxia, intention tremor, and choreathetosis which affects the cranial musculature predominantly but also that of the trunk and limbs. A coarse rhythmic tremor of the arms, appearing with certain sustained postures, mild pyramidal tract signs, and diffuse EEG abnormalities complete the clinical picture. Other less frequent signs are muscular rigidity, grasp reflexes, tremor in repose, nystagmus, asterixis, and in isolated cases an ataxic tremor that has been referred to by Lance and Adams (1963) as action myoclonus. In essence, each of the neurologic ab-