THE DIFFERENTIATION OF DELIRIUM TREMENS FROM IMPENDING HEPATIC COMA*

By

ESTHER A. DAVIDSON, M.B., M.R.C.P.E., D.P.M.

Research Fellow in Psychiatry
Harvard Medical School
Research Associate in Psychiatry
Boston City Hospital

and

PHILIP SOLOMON, M.D.

Assistant Clinical Professor of Psychiatry
Harvard Medical School
Physician-in-Chief for Psychiatry
Boston City Hospital

Introduction

The problem of differentiating impending hepatic coma from delirium tremens is one which arises less commonly in Great Britain than in the United States. It is a problem which occurs, of course, chiefly in connection with alcoholic patients and while alcoholism has declined in Great Britain it is becoming an increasing medical and social problem in certain sections of the United States (1). Thus, at the Boston City Hospital alcoholism was a factor in over 45 per cent. of patients with cirrhosis of the liver at post-mortem (2). At the Hammersmith Hospital in London alcoholism was an aetiological factor in 5 per cent. of patients with the clinical diagnosis of cirrhosis (3). There is no doubt that the problem of differentiating impending hepatic coma from delirium tremens is a common and relatively easy one in Boston, whereas in London it is a rare and therefore more difficult one.

The importance of differentiating these two conditions lies in the field of therapy, for what is appropriate therapy for the one condition may be lethal for the other. Treatment by tranquillizers and sedatives may precipitate terminal hepatic coma in the patient in whom coma is only impending. Even small doses may be lethal. Hydration therapy required for delirium tremens may also be fatal to the patient with impending hepatic coma. A high protein diet for supposed delirium tremens may precipitate a patient with impending hepatic coma into terminal coma. On the other hand, purging and a protein-free diet, appropriate for impending hepatic coma, may be disastrous for the patient with delirium tremens. It is therefore vital to the patient's welfare that the physician be able to distinguish between delirium tremens and impending hepatic coma. It is also important to recognize that both conditions may exist simultaneously.

Review of the Literature

Delirium tremens: "Laerian who lay sick in the house of Demaenatus was seized with fever after drinking. Third day acute fever, trembling of the head, particularly of the lower lip; after a while convulsions, complete delirium, an

* From the Psychiatry Service, Boston City Hospital and the Department of Psychiatry, Harvard Medical School.

uncomfortable night." So wrote Hippocrates (4) of a patient who may have been the first recorded case of delirium tremens. In 1813 Thomas Sutton (5), an English practitioner, first distinguished delirium tremens from other types of "brain fever" and suggested its relationship to chronic alcoholism. He said it occurred only in individuals "who had been drinking beyond moderation or propriety". In 1822 Hayward (6) attributed the condition to venous congestion of the brain, and nine years later Wake (7) confirmed Hayward's findings and observed that the prognosis depended on the severity of associated injuries or disease processes. Kraepelin (8) gave the classic description of delirium tremens as follows: disorientation in the three fields, "collectedness" and ability to converse normally, good memory for past events, mingling of false and true perceptions, vivid hallucinations of sight, half-apprehensive, half-humorous mood, restlessness, tremors, and the odour of alcohol. He believed that this clinical picture was pathognomonic of delirium tremens.

Wortis (9), in reviewing the post-Kraepelinian literature, mentioned that at various times psychogenic, metabolic, and personality factors have been implicated in the aetiology of delirium tremens. In recent years the withdrawal theory for the production of delirium tremens has gained prominence (10), but remains to be proved.

Under the heading of "the tremulous-hallucinatory-epileptic-delirious states", Victor and Adams (11) recognized the following syndromes: (1) alcoholic tremulousness, which constituted four-fifths of the group; (2) alcoholic hallucinosis; (3) alcoholic epilepsy; (4) Wernicke's encephalopathy; (5) typical delirium tremens, which is the rarest of these syndromes.

The last is characterized by psychomotor, speech, and autonomic over-activity, disorientation, confusion, and disordered sense perception.

Wortis gave the incidence of delirium tremens as 39·8 per cent. of all psychotic admissions to the Boston Psychopathic Hospital in 1940. In 1951, at the Boston City Hospital, 11,987 patients were admitted to the medical services. Of these, 1,622 (14 per cent.) suffered from some form of acute alcoholism; 236 of these (2 per cent. of the total, 15 per cent. of the alcoholics) had delirium tremens on admission.

The biochemical or metabolic disturbances underlying delirium tremens are not known but Fink (12) has recently claimed that low serum magnesium levels are frequently found in this condition. He believes that the syndrome of muscle tremor, twitching, bizarre movements, convulsions, anxiety, agitation, sweating, fever, tachycardia and severe delirium occurs in various states as well as in delirium tremens as a result of magnesium depletion secondary to inadequate magnesium intake.

Impending hepatic coma: In ancient cultures the liver was treated with the respect due to the seat of the soul (13) and in later eras its secretions were considered important in the differentiation of personality types on a humoral basis (14). The ancients recognized disturbed mental states complicating acute jaundice but it was not until the 18th century that the protean manifestations of hepatic coma were described. Excitement, delirium and a tendency to maintain abnormal postures were noted by early observers (15, 16) as associated symptoms in acute fatal jaundice, while Bright, in 1836 (17) described the monotonous speech and flexion attitudes which preceded coma. Bright was the first to recognize that delirium and tremor might occur in patients with hepatic cirrhosis as did Frerichs (18), but the tendency was to regard these as incidental symptoms of this disease or to ascribe them to alcohol as did Copland (19) and Rolleston (20).

The neurological signs of increased muscle tone (21), reflex changes (20), and extensor plantar responses (22) and ankle clonus (23) were added to the clinical picture. Green (24) stressed the important differences between the coma of hepatitis and of cirrhosis; the former characterized by abrupt onset, excitement and delirium foreign to the latter. Choreiform movements were first mentioned by Stokes, Owen and Holmes (25).

Zillig (26) and Adams and Foley (27) gave a comprehensive account of these characteristic features of hepatic coma and the latter stressed the diagnostic importance of the "flapping" tremor and EEG changes. Sherlock *et al.* (28), showed that the syndrome could exist in chronic form and introduced the concept of portal-systemic encephalopathy, relating the neuro-psychiatric disorder to a combination of hepato-cellular disease of varied aetiology, shunting of portal blood to the systemic circulation and the presence of nitrogenous substances in the gut (Fig. 1). Sherlock and her colleagues (29) also

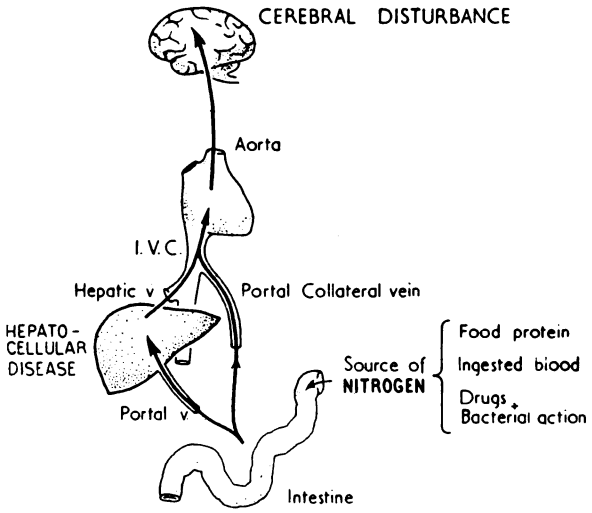

FIG. 1.—The mechanism of portal-systemic encephalopathy (Sherlock *et al.*, *Lancet*, *ii*, 453, 1954).

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showed that patients with the chronic syndrome may first be seen as diagnostic problems in mental hospitals, since mental disorder may dominate the clinical picture. Impending hepatic coma, no less in its acute than in its chronic form, can be regarded as the result of intestinal auto-intoxication by nitrogenous substances. It is indeed the toxic psychosis conceived of by Wagner-Jauregg (30) and elaborated on by Quastel (31).

MATERIALS AND METHODS

At the Hammersmith Hospital, London, 68 patients with hepatic coma or pre-coma, and one with hepatic coma and delirium tremens combined, were seen. More recently, at the Boston City Hospital, 15 patients with delirium tremens, 15 alcoholic patients with hepatic coma or impending hepatic coma, and 4 patients with both delirium tremens and impending hepatic coma were studied. Neuropsychiatric examination was carried out according to the schema

of Mayer-Gross and Guttmann (32). Case histories, data of physical status and results of laboratory tests were also acquired.

The neurological and psychiatric symptoms and signs were analysed in an attempt to delineate a characteristic picture for each syndrome. The details of this study and the actual statistical material have been omitted from this paper for the sake of brevity. It is planned that these will be published separately.

Results

1. Clinical Differentiation

(a) *Psychiatric Symptoms*

Delirium tremens and impending hepatic coma are both neuropsychiatric syndromes which may complicate chronic alcoholism. Each may follow a period of heavy alcoholic ingestion, but delirium tremens bears a more constant relationship to cessation of drinking, the symptoms occurring on the average three to four days after abrupt cessation. The alcoholic patient with impending hepatic coma may go on drinking even after he has become jaundiced and continue until he develops complete hepatic coma.

The patient with delirium tremens is fully conscious in that he responds to stimuli unless he has been sedated or tranquillized, in which case he may show impairment of consciousness similar to that which is an early manifestation of hepatic coma. Psychomotor activity is greatly increased in the patient with delirium tremens, whereas the patient with impending hepatic coma is usually akinetic with episodes of restlessness. Aggressive, destructive behaviour is much more common in the patient with delirium tremens. Hallucinations mainly of sight and hearing are invariable in delirium tremens but uncommon in impending hepatic coma, apart from simple visual hallucinations such as flashing lights and stars. When formed visual hallucinations occur in impending hepatic coma they usually take the form of simple wish-fulfilling fantasies such as seeing departed relatives. In delirium tremens the hallucinatory content is almost always of a terrifying nature and frequently involves unpleasant visions of animals. Anxiety and fear are prominent affects in the patient with delirium tremens but very uncommon in the patient with impending hepatic coma. The latter may show a euphoric or depressed mood, a genial euphoria being more common in the alcoholics with impending hepatic coma. At a later stage mental torpor and the desire not to be bothered distinguish the patient with pre-hepatic coma from the delirious alcoholic patient who is over-responsive to stimuli.

Occupational delirium as well as fragments of drinking behaviour such as ordering drinks, reaching for a glass, sipping movements are frequent components of delirium tremens. We have never observed such activities in impending hepatic coma.

(b) *Neurological Signs*

Tremor, not usually present at rest but present on intentional movement, characterizes both delirium tremens and impending hepatic coma. The tremor of delirium tremens is fine to coarse and rhythmic, while that of impending coma is typically irregular and "flapping". The "flap" may be absent in the alcoholic patient with impending hepatic coma. The speech in delirium tremens is rapid and elided. Sudden bursts of shouting in response to hallucinations interrupt conversation with the patient who is developing delirium tremens. The speech in impending hepatic coma is slow, slurred, and monotonous.

Perseveration of speech and aphasia, features of hepatic coma, have not been observed in delirium tremens.

Motor power is decreased in the patient with impending hepatic coma in association with pyramidal tract signs and possibly with a local disorder of muscle metabolism. Early symptoms of impending hepatic coma include complaints of weakness or easy fatiguability. At a later stage muscle weakness becomes intense and is associated with rigidity usually of a clasp-knife variety. Finally, flaccidity supervenes in terminal coma.

In delirium tremens the patient appears to be possessed of great muscular strength. Poised as he is for fight with or flight from the terrors that assail him, he is capable of muscular feats which at other times are beyond him. One patient with incipient delirium tremens was able to elude his real and imaginary pursuers in a dash through the streets of Boston, while another stated that he had broken the record for the mile run in his flight to the hospital. Exhaustion from over-activity is the greatest danger to life in delirium tremens.

Posture is unremarkable in delirium tremens except that the patient may not be able to maintain the standing position on account of tremor. Flexion attitudes are commonly seen in the patient with impending hepatic coma and a mask-like staring expression may be found in this condition. There is no obvious change in muscle tone in delirium tremens; in impending hepatic coma increased tone in the flexors is generally found. The tendon reflexes in the patient with delirium tremens usually show no change, though the ankle jerks may be absent if there is a peripheral neuropathy. On the other hand, the tendon reflexes are markedly increased in the patient with impending hepatic coma. Clonus develops irregularly and is associated with flexor plantar responses in the early stages, later with unilateral and then bilateral extensor plantar responses.

Sudden alcohol withdrawal following a period of heavy ingestion may produce symptoms of autonomic imbalance, premonitory to the development of alcoholic hallucinosis or delirium tremens. The earliest complaints are of restlessness, tension, and anxiety with chills and fever, and some degree of tremulousness, the "shakes". The face is flushed, there is tachycardia and sometimes auricular fibrillation. The appearance of cold sweats may coincide with relief from the anxiety and complete the withdrawal syndrome or the condition may progress. During the onset of delirium tremens the somatic accompaniments of fear may develop in association with hallucinatory episodes. One patient reported that he awoke to find his hair literally standing on end and immediately thereafter experienced frightening hallucinations. Such episodes may be combined with aggressive behaviour or with such precipitous flight from the terror that death may inadvertently occur.

The patient with impending hepatic coma slips into stupor usually without evidence of anxiety or fear. He is drowsy, though easily aroused, and appears preoccupied. His replies are short and polite and almost automatic. Low-grade fever may develop during episodes of coma and gross hyperthermia has been seen during terminal states. The patient with severe liver disease loses his ability to sweat. However, there is not the evidence of marked autonomic disturbance that is seen in the patient with delirium tremens.

Total insomnia is the rule in untreated delirium tremens with nocturnal exacerbation of symptoms, perhaps related to decreased sensory input (32). In impending hepatic coma hypersomnia gives place to reversal of sleep rhythm. Episodes of confusion with nocturnal wandering occur, but lack the affective

fire associated with the psychomotor discharges of the patient with delirium tremens.

Anorexia is a symptom of the alcoholic on spree as well as a major symptom of delirium tremens. The thirst for alcohol represents the only remnant of appetite. Fluids may be taken avidly if they are proffered as alcoholic beverages. In chronic impending hepatic coma in the non-alcoholic patient hyperphagia is common, sometimes as a perseveration of eating, as in the patient who devoured a complete round of sliced cake and rapidly became comatose, or as a vegetative symptom. Anorexia is found in the alcoholic patient with acute hepatic decompensation, and return of the appetite is always to be regarded as a good prognostic sign.

(c) *General Medical Symptoms*

The patient with delirium tremens is seldom visibly jaundiced although he may show slight elevation of the bilirubin level. The alcoholic patient with impending hepatic coma is usually deeply jaundiced as the result of acute hepatic decompensation following prolonged heavy drinking and poor diet. Fourteen of 15 patients with uncomplicated delirium tremens showed mild degrees of hepatomegaly in contrast to the hepatomegaly of the alcoholic in impending coma which was of gross degree and was usually associated with ascites and other evidences of acute hepatic decompensation. Splenomegaly is uncommon in impending hepatic coma of the alcoholic except in the more chronic types of hepatic coma where a portal-systemic shunt has developed, whereas it is common in the impending hepatic coma of the non-alcoholic.

The stigmata of liver disease; spiders, palmar erythema, loss of body hair, clubbing of the fingers, white nails, and multiple bruises, may be found in both delirium tremens and impending hepatic coma but such stigmata are likely to be more extensive in hepatic coma. In the alcoholic with liver disease, parotid enlargement, Dupuytren's contractures, pancreatitis, and macrocytic anaemia are frequently found and in the absence of a history, may distinguish the alcoholic from the non-alcoholic type of cirrhosis. Foetor hepaticus may be a feature of impending hepatic coma, but is never found in uncomplicated delirium tremens.

A condensation of the more useful distinctions in the clinical differentiation of delirium tremens from impending hepatic coma is presented in Table I.

TABLE I

Elements in the Clinical Differentiation of Delirium Tremens from Impending Hepatic Coma

	Delirium Tremens	Impending Hepatic Coma
Consciousness	+	−
Psychomotor activity	+	−
Anxiety	+	−
Tremor	Fine	Flap
Speech	Rapid	Slow
Hallucinations (formed)	+	−
Muscle strength	+	−
Autonomic imbalance	+	−
Jaundice	−	+
Sleep	−	+
Appetite	−	+

(+) Often present (−) Rarely present

2. Laboratory Differentiation

The laboratory can be of assistance in differentiating delirium tremens from alcoholic impending hepatic coma. Our data indicate that liver function tests show far more abnormality in alcoholic impending hepatic coma than in delirium tremens. The following tests were used: serum bilirubin, bromsulphthalein retention, prothrombin time, cephalin flocculation, and formol gel.

Additional laboratory findings were as follows: sodium, chloride, CO_2 combining power, and NPN were usually normal and potassium was usually low in both delirium tremens and in alcoholic impending hepatic coma. These findings, therefore, were not of help in the differentiation. Blood ammonia levels are usually elevated in alcoholic impending hepatic coma and normal in delirium tremens.

In the patients with both delirium tremens and alcoholic impending hepatic coma, liver function tests showed impairment similar to those patients with alcoholic impending hepatic coma alone.

Sensitivity to dietary protein is a diagnostic test for impending hepatic coma. If protein is ingested in gradually increasing amounts, there is no untoward effect in the patient with delirium tremens, but the patient with impending hepatic coma will become increasingly comatose as his protein tolerance is exceeded. A similar test may be done with ammonium chloride (29).

Recordings of electroencephalograms was not a routine procedure in the group of patients with delirium tremens. This procedure may be of value in differentiating delirium tremens from impending hepatic coma. Kennard *et al.* (33) have shown in delirium tremens low amplitude, increased amounts of fast activity, and low percentage of alpha rhythms. With symptomatic improvement the amount of fast activity decreased, slower alpha activity reappeared, amplitudes increased, and records became more regular. In impending hepatic coma in the Hammersmith series, slowing of the dominant rhythms from the alpha to the theta and delta ranges was associated with progression of coma. Although fast activity was seen it was by no means a prominent feature.

Summary

The differentiation of delirium tremens from impending hepatic coma is important since appropriate therapy for the one condition may be lethal for the other. The literature concerning the two conditions is reviewed.

Our own material comprises, at the Hammersmith Hospital, London, 68 patients with hepatic coma or pre-coma and one with hepatic coma and delirium tremens combined, and, at the Boston City Hospital, 15 patients with delirium tremens, 15 alcoholic patients with hepatic coma or pre-coma, and 4 patients with both delirium tremens and impending hepatic coma. Clinical study of these 102 patients reveals data which is of value in the differential diagnosis.

The data from our patients is organized and presented in this paper under the following headings:

1. Clinical differentiation: (*a*) Psychiatric symptoms; (*b*) Neurological signs; (*c*) General medical symptoms and signs.
2. Laboratory differentiation.

The more useful clinical distinctions are condensed and shown in the form of a Table.

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