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EDITORIAL

HEPATIC ENCEPHALOPATHY

'Appolonius at Abdara suffered for a long time without taking to his bed. He had an enlarged abdomen and a pain in the region of the liver to which he had become accustomed, for he became jaundiced, flatulent and of pallid complexion.

'As a result of eating beef and drinking cows' milk, he developed what was a slight fever at first and went to bed. He got much worse through taking a large amount of milk—and a generally bad diet. He began talking at random, showed loss of memory in anything he said, and became disorientated.

'About the fourteenth day—his temperature rose and he went out of his mind; there was shouting, disturbance and much talking, then he settled down again and relapsed into coma. Subsequently his bowels were upset. The excreta were not always the same; sometimes they were small in quantity and dark and rust-coloured or they were greasy, raw and pungent.

Thirty-fourth day: died.'

Hippocrates: Epidemics, Book III (*xiii*).[1]

Cerebral complications of liver disease have been recognized by physicians since antiquity. Modern literature includes references to the writings of Galen,[2] Boerhaave[3] and Morgagni[4] on this subject, and we quote above a case history from the works of Hippocrates which has particular interest in the light of recent concepts of the pathogenesis of this disorder.

The encephalopathy under consideration is a distinct entity and has been referred to as 'hepatic coma'[5] or as 'porto-systemic encephalopathy'.[6] It is to be distinguished from a number of other syndromes of cerebral disorder to which patients with liver disease are prone, e.g. Korsakoff's psychosis, Wernicke's encephalopathy, pellagrous dementia, subdural haematoma, intolerance of barbiturates, Kinnear Wilson's disease, and so on. It occurs most frequently in cases of hepatic cirrhosis and in severe infective or toxic hepatitis. It has also been reported with chronic obstructive jaundice, eclampsia, and abscess or metastatic carcinoma of the liver. In cirrhotic patients the syndrome is most often precipitated by haemorrhage from the upper alimentary tract. Diuretics, particularly ammonium chloride and ammonium-containing exchange-resins, abdominal paracentesis, intercurrent infection and acute alcoholism may also act as precipitants.

In fulminating hepatitis, the clinical picture usually develops rapidly; in the cirrhotics, however, a more

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HEPATO-ENCEPHALOPATHIA

‚Vir 'n lang tyd het Appolonius in Abdara gely voordat hy gaan lê het. Sy buik was vergroot en hy het 'n pyn in die lewerstreek gehad waaraan hy gewoond geraak het want hy het geelsug, winderigheid en 'n bleek gelaatskleur ontwikkel.

‚As gevolg van die beesvleis wat hy ge-eet het en die koeimelk wat hy gedrink het, het hy 'n ligte koors gekry en is hy bedtoe. Te wyte aan van die groot hoeveelheid melk wat hy gedrink het—en 'n swak dieet oor die algemeen—het sy toestand baie vererger. Hy het deurmekaar begin praat, geheueverlies getoon en het verward geword.

‚Ongeveer die veertiende dag—sy koors het gestyg en hy het van sy verstand geraak; hy het geskreeu, was oproerig en het baie gepraat, toe het hy weer bedaar en in 'n koma verval. Sy maag het begin werk . Die ontlasting was nie altyd dieselfde nie; somtyds was dit min en donker en roeskleurig, of dit was vetterig, rou en skerp.

Vier en Dertigste dag: gesterwe.'

Hippocrates: Epidemics, Book III (*xiii*).[1]

Serebraalkomplikasies wat op lewersiekte volg is al eeuelank aan geneeshere bekend. Hedendaagse literatuur oor hierdie onderwerp bevat verwysings na Galen[2] Boerhaave[3] en Morgagni[4] en hierbo het ons 'n gevallegeskiedenis uit die werke van Hippocrates aangehaal, wat besonder interessant is met die oog op die jongste opvattings in verband met die ontstaan van hierdie siekte.

Hierdie harsingaandoening is 'n duidelike entiteit en is na verwys as *hepatic coma*[5] of as *portosystemic encephalopathy*.[6] Dit moet onderskei word van 'n aantal ander sindrome van harsingstoornisse waartoe pasiënte met lewerkwale geneig is, bv. Korsakoff se psigosie, Wernick se harsingaandoening, *pellagrous dementia*, subdurale hematoom, onverdraagsaamheid i.v.m. barbiturate, Kinnear Wilson se skiekte en dies meer. Dit kom mees dikwels voor by gevalle van lewersirrose en by ernstige besmetlike of toksiese lewerontsteking. Dit is ook al aangeteken gepaard met kroniese verstoppende geelsug, stuipe en verswering of metastatiese karsinoom van die lewer. In sirrotiese pasiënte word die sindroom veral verhaas deur bloedstorting uit die boonste spysverteringskanaal. Uriendrywende middels, veral ammonium chloried en uitruilingsharssoorte wat ammonium bevat, buikparasentese, tussenkomende infeksie en akute dranksug kan ook die toestand verhaas.

As die lewerontsteking heftig is, ontwikkel die kliniese beeld gewoonlik snel; met sirrose is die proses gewoonlik meer gestadig. Kennisse van die pasiënt sal verandering in sy persoonlikheid bespeur; die vrolike, dranksugtige sirrotiese pasiënt word nors en kwaai; sy persoonlike gewoontes word slordig; hy ly aan nagmerries en sy

insidious onset is common. Those acquainted with the patient will observe a change in his personality; the cheerful, bibulous cirrhotic becomes morose and truculent; his personal habits become slovenly; he suffers from nightmares and his demeanour may vary from extreme lethargy to acute mania. In the established case, the hiccupping, grimacing or yawning patient characteristically lies in bed with his legs crossed and his knees drawn up onto his abdomen. He is often rowdy and may be violently restless. Consciousness may be simply clouded, sometimes with reversed sleep-rhythm, or the patient may be stuperose or in deep coma. Muscle twitchings or choreiform movements may be present, but most typical is the 'flapping tremor' first described by Adams and Foley[5] and likened by Sherlock[6] to the beating of a bird's wings. To elicit this sign the patient's hands are held outstretched in front of him and rapid irregular, asymmetrical flexion-extension movements of the wrists and metacarpo-phalangeal joints are observed. Further examination reveals variable, asymmetric spasticity of either pyramidal or extrapyramidal type, occasionally with extensor plantar responses. Roving eyeballs, dilated pupils, grasping or sucking reflexes and hyperpyrexia are other inconstant signs.

When liver function tests are made in these cases, biochemical disturbance is almost always demonstrated. The changes may be relatively slight and do not correlate in any linear fashion with the degree of neurological disorder. A more constant finding of great interest is the disturbance of ammonia metabolism,[7] manifested by an abnormally high ammonia-concentration in the peripheral blood and the cerebrospinal fluid. This finding provided the clue to the pathogenesis of the disorder.

It has long been known that dogs with 'Eck fistulae' (i.e. experimentally produced porto-caval anastomoses) develop neurological abnormalities when fed on meat.[8] In human beings with severe liver disease or with porto-caval shunts, similar disturbances may follow the ingestion of ammonia-containing substances.[9] Sherlock and her associates[6] have shown that these substances pass unmetabolized through the damaged liver into the systemic circulation or may actually by-pass the liver *via* porto-caval collaterals. The resulting excess of ammonia interferes with the delicate processes of cerebral metabolism and neurological symptoms ensue. Riddel[10] has suggested that ammonia disturbs the Kreb's citric-acid cycle by combining with α-ketoglutaric acid to produce glutamic acid; the latter is further aminated to produce glutamine, of which a considerable excess has been found in the cerebrospinal fluid of patients with hepatic encephalopathy.[11]

The primary pathogenic factor, therefore, is faulty metabolism of the nitrogenous material absorbed from the bowel, and a resemblance to the mellow concept of 'auto-intoxication' will be apparent. This is particularly striking in the recently recognized syndrome of 'chronic intermittent hepatic coma',[3] in which exacerbations of a chronic course are related to occult gedrag mag van uiterste letargie tot akute manie wissel. In gestaafde gevalle is dit kenmerkend om die hikkende, grynsende of gapende pasiënt in die bed te kry met sy bene gekruis en sy knië tot op sy maag getrek. Hy is dikwels lawaaierig en mag geweldig onrustig word. Hy mag net beneweld wees, somtyds met sy slaappatroon omgekeer, of die pasiënt mag in bewusteloosheid of in 'n diep koma versink. Spier- of senuweetrekkings mag aanwesig wees maar die mees tiperend is die ‚flapbewing' wat vir die eerste 6 keer deur Adam en Foley[5] beskryf is en deur Sherlock vergelyk is met die flap van 'n voël se vlerke. Om hierdie teken aan die lig te bring word die pasiënt se hande voor hom uitgestrek en vinnige, onegalige, asimmetriese buig-strekbewegings van die polsgewrigte en die middelhand-vingerlitte word waargeneem. Nadere ondersoek stel aan die lig wispelturige, asimmetriese spastisiteit wat òf primidiaal òf buiteprimidiaal is, af en toe met voetsoolstrekspierreaksies. Ronddolende oogballe, oopgerekte oogappels, klouende of suigende reflekse en hoë koors is ander tekens wat somtyds waargeneem word en ander tye nie.

Wanneer die lewerwerking in hierdie gevalle getoets word, word biochemiese stoornisse byna altoos ontdek. Die stoornisse mag betreklik gering wees en korreleer geensins lynvormig met die graad van neurologiese ongesteldheid nie. 'n Meer bestendige bevinding van groot belang is die steuring in die ammoniummetabolisme[7] wat geopenbaar word deur 'n abnormaal hoë konsentrasie ammonium in die perifeerbloed en in die harsing en rugmurgvloeistof. Hierdie bevinding is die leidraad tot die patogenese van hierdie ongesteldheid.

Dit is al vir 'n geruime tyd bekend dat honde met 'Eck fistulae' (d.w.s. poortholte-anastomose wat eksperimenteel verkry word) neurologiese abnormaliteite ontwikkel as hul op vleis gevoer word[8]. By pasiënte met ernstige lewerkwale of met poortholte-anastomose kan soortgelyke steuring op die inname van ammoniumbevattende stowwe volg.[9] Sherlock en haar medewerkers[6] het gevind dat hierdie stowwe sonder stofverwisseling deur die beskadigde lewer na die grootbloedsomloop passeer of dat dit selfs die lewer vermy en die ompad via die poortholte-kollaterale kies. Die oormaat ammonium wat hierop volg belemmer die delikate prosesse van serebraalmetabolisme en neurologiese simptome volg daarop. Riddel[10] meen dat die Kreb-sitroensuurkringloop verstoor word deurdat die ammonium met α-ketoglutaarsuur verbind om glutamiensuur te vorm; laasgenoemde word verder ge-amineer om glutamien te vorm waarvan 'n oormaat in die harsing en rugmurgvloeistof van pasiënte met hepato-encephalopathia gevind word.

Die belangrikste patogeniese faktor is derhalwe die gebrekkige metabolisme van die stikstofhoudende materiaal wat van die ingewande geabsorbeer word, en hierin word 'n ooreenkoms met die ou opvatting van selfvergiftiging ge-openbaar. Dit is besonder opvallend in die sindroom van ‚kroniese onderbroke hepatiese koma'[3] waarin 'n opvlamming van die kroniese verloop in verband staan met verborge of duidelike maagdermbloedstorting, maaltye van 'n hoë proteïengehalte, of inname van ammoniumsoutpurgasies.

Hierdie nuwe kennis van die ontstaan van die siekte beïnvloed nou die behandeling van die akute toestand.[12]

or obvious gastro-intestinal haemorrhage, to high-protein meals or to the ingestion of ammonium salts.

Treatment of the acute condition has been modified by this new understanding of its pathogenesis.[12] Restriction of nitrogenous intake and the inhibition of endogenous protein metabolism are regarded as fundamental. To this end, all nitrogen-containing substances—protein, amino acids and ammonia-containing medicaments—are eliminated from the diet. Bleeding oesophageal varices are occluded as quickly as possible by balloon tamponage,[13] and bacterial activity in the gut is retarded by large oral doses of a tetracycline antibiotic. Further 'de-amination' of the gut is attained by repeated enemata and purges of magnesium sulphate. Endogenous protein metabolism is depressed by a high oral or parenteral carbohydrate-intake and by vigorously combating any infection. The patient's fluid and electrolyte requirements are sedulously maintained; supplemental vitamins, including vitamin K, are administered and sedation, when necessary, is achieved with paraldehyde. Intravenous transfusions of whole blood for post-haemorrhagic shock or anaemia are not contra-indicated. Finally, when clinical improvement occurs, protein is gradually brought back into the diet and the patient's tolerance is assessed. Most cases of hepatic cirrhosis can take about 50 g. of protein daily without neurological upset.

Walshe has postulated that glutamic acid converts the noxious ammonia into inert glutamine, and that a relative deficiency of glutamic acid occurs in ammonia intoxication. He therefore treated a small group of cases of hepatic coma with glutamic acid and reported good results.[14] Several other workers have failed to confirm these results,[10] but Ridell[9] is of the opinion that glutamic-acid therapy may benefit some cases of hepatic cirrhosis with encephalopathy.

The prognosis of this condition until recently was uniformly dismal. Encouraging results with the therapeutic regime outlined above, however, have emphasized the need for the more frequent and earlier diagnosis of the disorder.

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3. Sherlock, S. (1955): Brit. Med. J., **1**, 1383.
4. Foulk, W. T., Butt, H. R., Stauffer, M. H., Baggenstoss, A. M. and Gross, J. B. (1955): Gastroenterology, **29**, 17.
5. Adams, R. D. and Foley, J. M. (1949): Trans. Amer. Neurol. Assoc., **74**, 217.
6. Sherlock, S., Summerskill, W. H. J., White, L. P. and Phear, E. A. (1954): Lancet, **2**, 453.
7. van Caulaert, C. and Deviller, C. (1932): C.R. Soc. Biol., **111**, 50.
8. Balo, J. and Korpassy, B. (1932): Arch. Path., **13**, 80.
9. McDermott, W. V. and Adams, R. D. (1954): J. Clin. Invest., **33**, 1.
10. Riddel, A. G. (1955): Postgrad. Med. J., **31**, 389.
11. Whitehead, T. P. and Whittaker, S. R. F. (1955): J. Clin. Path., **8**, 81.
12. Sherlock, S. (1955): *Diseases of the Liver and Biliary System*, p. 143. Oxford: Blackwell Scientific Publications.
13. Blakemore, A. H. (1954): N.Y. St. J. Med., **54**, 2057.
14. Walshe, J. M. (1953): Lancet, **1**, 1075.

Die beperking van die inname van stikstofhoudende stowwe en die onderdrukking van proteïenmetabolisme wat inwendig ontstaan, word nou as fundamenteel beskou. Met hierdie doel voor die oë word alle stikstofbevattende stowwe—proteïen, aminosure en ammoniumbevattende geneesmiddels—uit die dieet geskakel. Bloedstortende slukdermspatare word so spoedig moontlik deur middel van ballontampons afgesluit[13] en die werking van bakterië in die derm word vertraag deur groot mondelinge dosisse van 'n tetrasiklien-antibiotika. Die derm word verder ‚ont-amineer' deur herhaaldelike enamata en purgasies van magnesium sulfaat. Endogene proteïenmetabolisme word onderdruk deur 'n hoë mondelinge of buitedermse koolhidraat-inname en deur kragdadig die hoof aan enige infeksie te bied. Die pasiënt se vloeistof- en elektrolietbehoeftes word sorgvuldig in voorsien; aanvullende vitamiene, veral vitamien-K, word toegedien en indien kalmering nodig is word paraldehied gebruik. Daar is geen teenaanwysing nie vir binneaarse bloedoortapping met heel bloed om bloedarmoede of skok wat op bloedstorting volg te bestry nie. Ten slotte, wanneer kliniese verbetering intree, word proteïen geleidelik in die dieet teruggebring en die pasiënt se dulding daartoe getoets. Die meeste gevalle van hepatiese sirrose kan omtrent 50 g. proteïen daeliks inneem sonder enige neurologiese stoornisse.

Walshe postuleer dat die glutamiensuur die skadelike ammonium in logge glutamien omskep en dat 'n relatiewe tekort aan glutamiensuur by ammoniumvergiftiging voorkom. Hy het derhalwe 'n klein groep pasiënte met hepatiese koma met glutamiensuur behandel en goeie resultate noteer.[14] 'n Heel paar ander navorsers kon hierdie resultate nie staaf nie[10] maar Ridell[9] meen dat glutamiensuurterapie sommige pasiënte wat ly aan hepatiese sirrose met encephalopathia kan baat.

Tot onlangs was die prognose vir hierdie kondisie deurgaans somber. Die belowende resultate wat verkry word met die behandeling wat hierbo uiteengesit is, beklemtoon die noodsaaklikheid om die ongesteldheid meer dikwels en vroeer te diagnoseer.

1. Chadwick, J. en Mann, W. N. (1950): The Medical Works of Hippocrates, p. 77. Oxford: Blackwell Scientific Publications.
2. Walshe, J. M. (1951): Quart. J. Med., **20**, 421 (N.S.).
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