BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 31 1942

THE SYNDROME OF PERIODIC SOMNOLENCE AND MORBID HUNGER (KLEINE-LEVIN SYNDROME)

BY

MACDONALD CRITCHLEY, M.D., F.R.C.P.

Surgeon Captain, R.N.V.R.

AND

H. LOVELL HOFFMAN, M.B., B.Ch., M.R.C.P.

Surgeon Commander, R.N.V.R.

In W. Kleine's report (1925) upon a series of five cases of periodic somnolence there were two patients in whom bouts of hypersomnia were associated with excessive appetite. Four years later M. Levin (1929) included in a paper entitled "Narcolepsy and Other Varieties of Morbid Somnolence" another case in which symptoms of polyphagia and pathological sleep periodically occurred in combination. In 1936 the same author, having collected seven such cases from the literature and from his own observation, published them as examples of a new syndrome of "periodic somnolence and morbid hunger." This syndrome was considered to occur exclusively in males, starting in the second decade, and to be characterized by attacks of sleepiness lasting several days or weeks, associated with excessive hunger, motor unrest, and various psychological features, notably irritability, mild confusion, incoherent speech, and, at times, hallucinations. Three of the patients developed their initial symptoms soon after an acute illness ("grippe," tonsillitis, influenza). Levin's paper did not attract much notice, as judged by the lack of fresh case records by other physicians. Another of his publications upon this subject (Levin, 1938) did not contain any new clinical material.

We here report two more cases of periodic somnolence and morbid hunger typical of the syndrome described by Kleine and by Levin, with special reference to blood-sugar estimations and, in one case, to the electro-encephalographic findings.

Case I

The patient, an air mechanic aged 20, was admitted to a naval hospital on April 21, 1941. Apart from measles no illness had occurred. The family history revealed no nervous or mental disease.

History of the Illness.—In 1937, after re-vaccination, the patient developed generalized vaccinia, but showed no symptoms suggesting encephalitis. Six months later there started attacks of drowsiness lasting about three days at a time. These recurred every six to nine months, though the interval between the last two attacks was one year. His first attack began just before his midday meal, at a time when he was working at a rather uncongenial job on radio research. He attributed his attacks to overwork, either physical or mental. In his bouts of somnolence he would spend most of his time asleep, though he could be roused quite easily. By dint of physical activity he could manage to keep himself awake. He did not yawn or feel "sleepy," but felt that he must shut his eyes, and then he would drop off to sleep at once. He has slept at work but never at meal-times, and in trains, but has never passed the proper station. He has never fallen asleep standing up. He thought that possibly his attacks were worse in the mornings. So far as he knew his diurnal sleep resembled his ordinary sleep, and he did not dream. During these bouts of sleepiness and while he was actually awake his mind was confused: in his own words: "My mind feels funny; my thoughts are not connected; I know what is happening, but the events do not seem to connect; I am somewhat muddled." Apparently he looks and behaves sensibly in these attacks. He does not complain of physical discomfort and is not troubled with unpleasant thoughts. At night his sleep is normal; there is no delay in getting off to sleep, and there are no hypnagogic hallucinations; nor is there anything to suggest "sleep paralysis" either in the night or on waking. During the whole of his bout of sleepiness his appetite is excessive, but there is no undue thirst. Gradually the attack of sleepiness wears off and he comes round feeling none the worse. In other respects his health is exceptionally good. He is athletic in habits and his weight has remained stationary. There is nothing whatever in his history to suggest attacks of cataplexy, occurring either spontaneously or as a result of emotion or sudden noise.

Those who had the opportunity of seeing him during one of his attacks reported that he became progressively more drowsy over the course of two days. His instructor found him so sleepy in classes that he referred him to the medical officer. While under medical observation he remained asleep almost the whole of the time, waking, however, for meals. He showed no obvious abnormal behaviour, and no delusions or hallucinations. When roused and questioned he appeared well orientated, but slow in cerebration, having difficulty in translating his thoughts into speech. He sometimes walked round the ward half asleep. There was no motor restlessness or agitation. On the day of admission he could give a satisfactory and detailed account of himself, but could not describe the actual thoughts that occurred during his bouts. His temperature remained normal throughout five days in hospital. His last period of hypersomnia lasted altogether about a week.

Physical Examination.—His general appearance was quite normal; the facies did not suggest Parkinsonism, and there was no tremor. No abnormal physical signs were found in the heart, lungs, abdomen, or central nervous system. Blood pressure was 120/75.

Special Examinations.—Urine: acid, specific gravity 1018; no albumin or sugar. Blood Wassermann reaction: negative. Radiographs of the skull showed no abnormality, the pituitary fossa being regular in outline and within normal limits of size and shape. An electro-encephalogram revealed no abnormality while resting, and the alpha rhythm was normal in every respect. Vigorous overbreathing evoked a large intermittent delta dis-

charge involving both frontal lobes, but this was more regular on the left. The blood-sugar curve was: fasting, 71.4 mg. per 100 c.cm.; 1/2 hour after ingestion of glucose, 87.7 mg.; 1 hour after, 108.7 mg.; 1½ hours after, 113.6 mg.; 2 hours after, 82.3 mg. This showed a somewhat low fasting level, but on the whole the curve can be regarded as normal. The patient was given a low carbohydrate diet (80 grammes a day) and was made to do strenuous physical training. No abnormal symptoms developed during this period. An insulin-tolerance test was then carried out according to the technique recommended by Dr. Russell Fraser (1938, 1941), to whom we are indebted for help in this case. A diet of 400 grammes of carbohydrate was given daily for three days, followed by twelve hours' fasting. Seven units of insulin (0.1 unit per kg. body weight) was given intravenously and blood-sugar estimations were made at various intervals thereafter. There was some fall in blood pressure and pulse rate, also slight drowsiness and hunger, but no other abnormal symptoms occurred. The blood-sugar readings showed a normal response to the test. They were: resting level, 95 mg. per 100 c.cm.; twenty minutes after injection of insulin, 43 mg.; at 30 minutes, 43 mg.; at 40 minutes, 62 mg.; at 60 minutes, 62 mg.; at 90 minutes, 82 mg.; at 120 minutes, 96 mg.

Case II

The patient, a man aged 25, was admitted to a naval hospital on July 2, 1941. According to the records, he had been having attacks of sleepiness since 1933. These would occur every few months, and lasted a few days at a time. The patient knew of no precipitating factor and there was no history of any illness shortly before the first of his attacks. Each bout consisted of extreme sleepiness, together with some confusion and a very definite excessive hunger. For about two days after each attack he would be very depressed and oblivious of the events which messmates have commented that he "rambled." So far as he knew, he was not restless or irritable during his attacks, but his messmates have commented that he "rambled.'" So far as he can tell, he showed the normal appearance of one in a state of sleep. There was no alteration in his nocturnal sleep either in an attack or in the intervening periods.

The first of his turns took place in January, 1933, four years before entering the Royal Navy. He was treated at St. Thomas's Hospital for ten days. He came into the Service in February, 1937, and in June of that year entered a naval hospital for a few days in a very sleepy state. No definite diagnosis was made. A rating in his ship declares that he saw the patient in another such attack in barracks in June, 1937, and this was witnessed at that time by a medical officer. There is also some evidence of another bout of hypersomnia in November, 1937. Yet another turn in January, 1938, while abroad, lasted six days and caused him to be sent to hospital, where he was fully investigated. He was readmitted to the hospital on July 8 of that year. The medical officer of his ship had noted that on July 4 he complained of feeling "out-of-sorts" and was constipated. The same evening he became sleepy, and thereafter slept almost continuously. It was stated that when roused he was quite rational but that he quickly lapsed into sleep again.

He was invalided home from the Mediterranean Station on July 23, 1938, and was in an auxiliary hospital from August 8 to September 27, 1938. No drowsiness occurred during his stay there. A lumbar puncture yielded a fluid which was under normal pressure. It contained 3 cells per c.mm. and 30 mg. of protein per 100 c.cm. The Wassermann reaction and Lange's test were both negative.

While an in-patient in July, 1941, a glucose-tolerance test was carried out, with the following result: resting blood sugar, 76 mg. per 100 c.cm.; 1/2 hour after ingestion of glucose, 130 mg.; 1 hour after, 128 mg.; 1½ hours after, 102 mg.; 2 hours after, 72 mg. No glycosuria occurred. He was now put on a diet containing 400 grammes of carbohydrate a day, and after three days he fasted for twelve hours. He was then given an intravenous injection of insulin (0.1 unit per kg. body weight), and blood-sugar estimations were carried out, with the following result: 20 minutes after injection of insulin, 53 mg. per 100 c.cm.; at 30 minutes, 64 mg.; at 45 minutes, 64 mg.; at 75 minutes, 64 mg.; at 105 minutes, 64 mg. No somnolence or any other symptoms developed during this test.

Discussion

Both of these patients conform to the syndrome of periodic somnolence and morbid hunger as described by Kleine, but more especially by Levin. As to the pathogenicity of the condition, Levin is of the opinion that there is a periodic excess of inhibition exerted by the highest cerebral centres in these patients, including those centres controlling gastro-intestinal motility. In support of this view he quotes Fulton (1934), who found that appetite increased after bilateral removal of parts of the frontal lobes in monkeys. Many of these animals died of intussusception, which suggested gastro-intestinal hypermotility. Mettler *et al.* (1936) apparently demonstrated by radiographs similar hypermotility after removal of frontal cortical tissue in cats. Gastro-intestinal hypermotility is considered by Levin to be the cause of increased appetite, and therefore, on the basis of some frontal lesion, the symptom of morbid hunger is explained. By comparison with normal sleep he also attributes the somnolence to loss of function of the highest cerebral centres, which by releasing their control over lower centres produce the "motor unrest" which sometimes occurs in these patients; but it is not clear from his arguments why this motor unrest does not occur in physiological sleep. He quotes cases in which hunger has preceded or followed the ordinary paroxysmal sleep attacks of narcoleptics. He again explains this, in the light of Fulton's work, by assuming that the highest centres do not all undergo inhibition at the same moment, and that the centre for inhibition of gastro-intestinal movements goes into action at a different time from the other higher centres. Similarly, he tries to explain the pre-dormital paralysis of narcoleptics by suggesting that "the motility substrate has undergone inhibition in advance of the substrate of consciousness." Believing that the lesion producing morbid hunger is situated in the frontal lobes, Levin cites as additional evidence the case of an epileptic woman who was extremely hungry in her post-epileptic stupor. Preceding her fits, this woman had an aura of a "light-headed" feeling in the forehead. Levin remarks that "the significant thing is that the aura was felt in the forehead. It is possible that the sensation was referred from centres in the frontal lobes." Speculation of this kind is of course without scientific justification.

From a study of our own cases we can form no definite conclusion as to the morbid anatomy and physiology of the Kleine - Levin syndrome. Despite the electro-encephalographic findings in Case I, the suggestion of a frontal lobe dysfunction is by no means convincing, and it is far more tempting to visualize a patho-physiological process within or near the hypothalamus. We were unfortunate in not seeing the patients during their actual attacks, when blood-sugar and electro-encephalographic studies might have produced more helpful data.

The possibility of hyperinsulinism due to primary pancreatic overactivity can be dismissed, as none of the criteria laid down by Wilder (1940) for the diagnosis of this condition were fulfilled. These criteria are: (1) a post-absorptive blood sugar of less than 50 mg. per 100 c.cm.; (2) symptomatic attacks of hypoglycaemia occurring only when the patient is fasting; and (3) relief of such attacks by the administration of sugar. Although Wilder (p. 362) does not place much reliance on the glucose-tolerance and insulin-tolerance tests in hyperinsulinism, Fraser, who saw the charts of these tests in our first case, expressed the opinion that the results were strong evidence against hypoglycaemia being responsible. Moreover, apart from drowsiness and hunger, there were no other symptoms of hypoglycaemia in our patients.

Although it is idle to speculate without the evidence of blood-sugar estimations carried out in an actual attack, it is unlikely that a cerebral lesion—of the hypothalamus, for example—had caused temporary hypoglycaemia in these cases. Such a lesion, if it were to produce hypoglycaemia, would almost certainly also produce intolerance to insulin, which was not present in our cases. Confirmation of this statement is obtained from a study of the work of Cleveland and Davis (1936), who found insulin intolerance in 12 out of 14 cats with artificially produced hypothalamic lesions.

From those cases in which the syndrome of periodic somnolence and morbid hunger is preceded by an acute infection it is tempting to suggest that some form of mild encephalitis occurs which causes instability of the higher cerebral centres. The syndrome, however, does not appear to be related in any way to epidemic encephalitis. Narcolepsy—a much commoner cause of pathological sleep—differs from the present syndrome in many important features: (1) the attacks of sleep are shorter and more frequent, being paroxysmal rather than periodic; (2) excessive hunger does not typically occur; (3) cataplexy is a characteristic concomitant; and (4) disordered nocturnal sleep is usually present. It is not clear whether the hallucinations described in the Kleine-Levin syndrome are similar to the hypnagogic hallucinations of narcolepsy.

The result of electro-encephalography in Case I cannot be taken as conclusive evidence that a frontal lesion is responsible for the symptoms. (So far as we know, this is the only patient with the disorder to be examined by this means.) If subsequent cases also produce similar results this will be of considerable interest. The result obtained was similar to those found in cases of epilepsy or in patients with an epileptic predisposition who have never had fits. A finding of this sort probably indicates the existence of a cerebral dysrhythmia and nothing more.

Summary and Conclusions

The syndrome of periodic somnolence and morbid hunger is described, with special reference to the work of Levin.

Two cases are reported which have recently been observed in Royal Naval hospitals, in one of which there was an abnormal electro-encephalographic reading.

These cases, in our opinion, give strong evidence that such a syndrome exists as a definite entity.

Levin's views as to the cause of the syndrome are discussed, but it is considered that the nature of the pathological process is still obscure.

The differential diagnosis is considered with special reference to hypoglycaemia.

For permission to quote these two cases we are indebted to the Surgeon Rear-Admirals at the naval hospitals concerned.

REFERENCES

Cleveland, D., and Davis, L. (1936). *Brain*, **59**, 459.
Fraser, R., Maclay, W. S., and Mann, S. A. (1938). *Quart. J. Med.*, n.s., **7**, 115.
—— Albright, F., and Smith, P. H. (1941). *J. clin. Endocrinol.*, **1**, 297.
Fulton, J. F. (1934). *J. Mich. State med. Soc.*, **33**, 175.
Kleine, W. (1925). *Mschr. Psychiat. Neurol.*, **57**, 285.
Levin, M. (1929). *Arch. Neurol. Psychiat.*, **22**, 1172.
—— (1936). *Brain*, **59**, 494.
—— (1938). *J. nerv. ment. Dis.*, **88**, 414.
Mettler, F. A., *et al.* (1936). *Arch. Surg.*, **32**, 618.
Wilder, R. M. (1940). *Clinical Diabetes Mellitus and Hyperinsulinism*, Saunders, Philadelphia.

T. Brander (*Nordisk Med.*, 1941, **8**, 2547) records two fatal cases of varicella in children aged 2 months and 1 year respectively, who developed the eruption during convalescence from double pneumonia and were living under unfavourable sanitary conditions. One had a scarlatiniform eruption at the onset of the disease and the other had haemorrhages in the pocks. The varicellar lesions soon became necrotic and the subjacent muscle was invaded. Death from septicaemia ensued on the twenty-fifth and seventh days of disease respectively.

HEAVY PERCAINE SPINAL ANAESTHESIA

EXPERIENCE GAINED IN A SERIES OF 420 CASES

BY

WILLIAM W. MUSHIN, M.B., B.S., D.A.

Honorary Anaesthetist, Seamen's Hospital, Greenwich, and Central London Throat, Nose and Ear Hospital; Anaesthetist, Royal Dental Hospital; Anaesthetist, E.M.S.

Hypobaric, or light, solutions for spinal anaesthesia are losing their erstwhile popularity. Such techniques as those of Howard Jones (1930), Etherington Wilson (1935), and Lake (1938), though excellent in expert hands, are complex, and failure easily results if details are neglected. To-day, heavy, or hyperbaric, solutions are being increasingly used, by virtue of their simplicity of technique, constancy of result, and safety.

This paper records the experience gained in a personal series of 420 cases over a period of three and a half years, in which heavy percaine (1 in 200, in 6% glucose) was used, with no deaths and few complications. The technique evolved, though based on that described by Silverton (1934), differs from it in certain respects. The greater part of this work was carried out at the Seamen's Hospital, where the patients were men of excellent physique in whom the production of muscular relaxation by the use of general anaesthesia would have been a problem. It is one of my purposes to point out that it is particularly in such "good risk" cases that spinal anaesthesia produces its most gratifying results.

Behaviour of Heavy Solutions in the Subarachnoid Space

Solutions heavier than cerebrospinal fluid reaching the cephalic side of the lumbo-sacral projection tend, in the supine patient, to gravitate towards the mid-thoracic region. The number of nerve segments affected when a small volume of solution is introduced (1 to 2 c.cm.) depends chiefly on the quantity of drug, because as the solution moves towards the upper dorsal region the drug is being removed from the C.S.F. by both the nerve roots and the blood stream. In any case, it will not travel further than the lowest part of the dorsal curve unless there is still unabsorbed drug left at this point and the patient is steeply tilted head down. Thus sensory loss tends to stop automatically at about the level of D 6 to D 7 (ensiform), with motor loss one or two segments below this because posterior root effect is predominant when the solution stays in the dependent part of the thecal space. Thus two safety factors are inherent in the use of heavy solutions: the dorsal curve, limiting upward spread in the supine patient, and gravity, which limits anterior root involvement, with consequent less intercostal and sympathetic paralysis. If the patient is sitting up, a heavy solution sinks to the lowest part of the thecal sac, affecting the sacral roots only. There are thus two levels of anaesthesia, which automatically adjust themselves: one to the ensiform, suitable for lower abdominal surgery; the other to the "saddle" area, suitable for perineal operations.

Objections to Heavy Solutions Answered

Objections (e.g., Lake, 1938) to heavy solutions have been the "lack of control," and the danger of using the Trendelenburg position early in the operation.

"*Lack of Control.*"—This suggests that the anaesthesia may ascend too high; but the difficulty I have experienced with heavy percaine has been to get the solution to ascend higher than D 6 to D 8 by gravity alone. For upper abdominal anaesthesia it has had to be supplemented with barbotage (or mixing with C.S.F.). The only control between the limits of