ARSENICAL ENCEPHALOPATHY

A NOTE ON THE CONDITION STRESSING THE VALUE OF POSTURAL TREATMENT, WITH CASE RECORDS

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During an 18-months period—April, 1943, to Sept., 1944—in an area where malaria is hyperendemic and its cerebral manifestations severe and often fatal, it was expedient for us to form a "coma team" analogous to Sir Leonard Rogers's cholera team. This team has treated, in a small ward equipped for the purpose, 155 cases of fully developed coma attributable to malaria in Indian other ranks and camp followers. In addition to malarial coma, cases of coma due to such causes as uraemia, cholaemia, etc., and on five occasions following the injection of arsenicals, have been seen. That these five patients recovered, while at the same time the majority of similar cases occurring in other units terminated fatally (Davies, 1944), is attributed by us to the use of postural treatment in nursing. Support for this assertion, though not conclusive, may be drawn from the fact that in another hospital five cases treated on orthodox lines ended fatally; a sixth case was seen by one of us (J. C. S. P.) some hours after the onset of coma with convulsions. This patient finally recovered on the adoption of the method of treatment outlined below.

Originally devised to prevent the onset of pulmonary oedema, so common in malarial coma, nursing these patients in the sitting posture not only was found to prevent the onset of pulmonary oedema but appeared significantly to modify the depth of coma and the final outcome. The rationale of this procedure is dealt with in the discussion. We will here give a brief description of the condition and our method of treatment.

Description of the Condition

Arsenical encephalopathy—synonyms of which are arsenical serous apoplexy (Lees, 1937), arsenical haemorrhagic encephalitis, and arsenical encephalorrhagia—has occurred in 1.3% of the patients treated for syphilis by the rapid five-day method of administration of mapharside, and has been found to occur in the Army, using neoarsphenamine, and particularly in Tamil patients, with sufficient frequency to merit the most serious attention of all medical officers.

The following description of the pathology is that of Kinnier Wilson (1940). Perusal of the recent literature, of current textbooks, and of fatal case-sheets has added but little to his account of the clinical and histological features.

According to the English Salvarsan Committee's Report,¹ about 50% of "salvarsan deaths" in all countries have been due to a "haemorrhagic encephalitis," distinguished by abundant small perivascular effusions (mostly of the ring type), plugged capillaries with minute necrotic zones around them, and sometimes incomplete parietal occlusion in larger vessels; on occasions these thrombi are hyaline (Lissauer,² von Marschalko,³ Scott and Moore⁴). Interstitial reactions otherwise (cellular infiltration of vessel coats rather than of perivascular spaces) are never pronounced and frequently lacking.

Multiple minute capillary and pericapillary lesions of this kind, with hyaline thrombosis, are found also in carbon monoxide poisoning and narcosis, and were observed during the war in phosgene-gas cases. They occur, too, in cerebral malaria, fat embolism, and other disease conditions.

Subpial extravasation may accompany the cerebral, which is often well seen in optic thalami, cornu Ammonis, tegmentum, pons, and elsewhere (Scott and Moore, Globus and Ginsburg,⁵ Pollak and Riehl⁶). At times, however, nothing more than congestion and oedema is discovered (Obermiller,⁷ Stuhmer⁸). Moderate demyelination round haemorrhagic zones was remarked by Strauss and Globus.⁹

¹ M.R.C. Rep., No. 66, 1922 (lit.).² *Ibid.* W., xliii, 1917.³ *Ibid.*, xxxviii, 1912.⁴ *A.J.S.*, 1928.⁵ *A.N.P.*, xxx, 1933.⁶ *Jahrb. P.N.*, xlvii, 1930.⁷ *B.k.W.*, 1, 1913.⁸ *M.m.W.*, lxvii, 1919.⁹ *J.N.M.D.*, lxxv, 1930.

Examination of the cerebrospinal fluid shows that initially the pressure is normal. Later, as secondary cerebral oedema sets in, the pressure tends to rise. This also occurs in cerebral malaria. Protein varies from 40 to 300 mg. per 100 c.cm. Globulin is increased, but less so than in infective conditions—e.g., acute anterior poliomyelitis. The cells are usually normal; rarely are there red blood cells.

Aetiology

The causal factor is unknown. Apparently it is (1) not related to the arsenic radical, since poisoning by inorganic arsenic does not give rise to cerebral symptoms (Halcrow, 1943); (2) not related to dosage (Anwyl-Davies, 1941) (nevertheless the high incidence in the rapid mapharside method of treatment must be kept in mind); (3) not due to the Jarisch-Herxheimer reaction, since arsenical encephalopathy has occurred in non-syphilitics (Lees, 1937; Glaser, Imerman, and Imerman, 1935).

There may be some relationship to arsenical purpura—the disintegration of the arsenobenzene compounds in the blood being a possible factor (Halcrow, 1943). Further investigation of this is required. The tourniquet test, bleeding time, and platelet counts should be done in all cases; the very few that we have done so far have been normal.

The fact that recent cases have been described as occurring during pregnancy (Tzanck and Lewi, 1939; Nelson, McGibbon, and Glyn-Hughes, 1943), and the high incidence in Tamils (Davies, 1944), suggest the possibility of a protein or other dietetic deficiency. The work of Vail (1941) on the increased sensitivity to arsenic in the presence of hypovitaminosis-C, and of Horne and Scarborough (1940) on the value of hesperidine (vitamin P) in the treatment of arsenical purpura, is of the greatest interest in this connexion.

Symptomatology

Signs and symptoms usually appear after 2 to 4 injections of the first course of treatment, and may be associated with irregularity in treatment. They begin 1 to 4 days after the last arsenical injection—commonly the second—when headache, vomiting, and delirium are succeeded by deepening coma, a rising temperature, and death. Focal lesions, such as Jacksonian fits, facial palsy, external and internal ophthalmoplegias, have all been observed, as has also a meningitic reaction, although rarely. In cases which recover there may be transient mental and bizarre neurological pictures. These normally pass off after a few days.

Relation of Symptoms to Lesions.—The stage of irritability, headache, fits, and nausea corresponds to the initial vascular lesions. Deepening coma and death appear to be due to acute reactive oedema of the brain.

The average mortality rate is 75% (Kinnier Wilson). In recent literature 34 cases have been described, with 25 deaths; the mortality rate in military practice seems to have approximated this figure.

Diagnosis

Diagnosis may be facilitated by checking the field service card (IAFM 1272), usually carried in the pay-book, and by looking for needle marks in arms and buttocks. Cases are sometimes mistaken for other forms of encephalitis, cerebral malaria, cerebrospinal meningitis, benign lymphocytic meningitis, poisoning by drugs, alcoholism, epilepsy, and hysteria. Of these, in view of the fact that cerebrospinal meningitis will be excluded by lumbar puncture, cerebral malaria is by far the most important, and if the patient comes from a malarious area he must always be rigorously treated for this, irrespective of whether the clinician thinks that the case is one of arsenical encephalopathy or not.

Arsenic and Malaria.—There is evidence to show that the organic arsenicals can reactivate latent malaria, and cases of cerebral malaria have been recorded in which there were negative blood slides and positive brain smears after arsenical administration (Castellani, Marinesco, and Draganesco; quoted by Anderson, 1927). One so-called case of "arsenical encephalitis" in this army, which received no antimalarial therapy, was proved later to have been malarial in origin.

Principles and Practice of Treatment

The principles of treatment are: (1) to prevent, so far as is possible, the onset of secondary cerebral oedema and exudation through damaged capillaries; (2) to inactivate circulating arsenical drugs; (3) to observe the principles of nursing coma cases; (4) to anticipate complications—e.g., hyperpyrexia, convulsions, pulmonary oedema, pneumonia; (5) in malarious areas and in patients who have returned from malarious areas, treatment must be as for cerebral malaria.

Oedema of the brain in the past has been successfully relieved by repeated lumbar punctures combined with venesection. In view of the fact that in the prone position venous and hence capillary pressures are 80 to 100 mm. of water, while in the sitting patient they are negative to atmospheric pressure, "decongestion" can be achieved simply by nursing the patient sitting up, using a back-rest. The cerebrospinal-fluid pressure at ventricular level then drops to atmospheric level or less.

Postural nursing is the greatest single factor in saving life, and should be used in every case from the onset.

Lumbar puncture should be done initially for diagnostic purposes and the pressure, if raised, reduced to 100 mm. of water. This should be repeated if in spite of postural nursing the coma appears to deepen. A cisternal puncture is often more convenient.

Dehydration of the brain is indicated only if the coma is deepening in spite of postural nursing and lumbar punctures. It is done as for head injuries: (i) Concentrated serum albumin, 25% solution intravenously (U.S. Naval package: 25 g., equal to 450 c.cm. of plasma), is the method of choice. (ii) Failing the above, concentrated glucose-saline as supplied by the Army, 60 to 120 c.cm. intravenously, or hypertonic glucose solution (or sucrose, if available) by slow drip infusion.

Sodium or calcium thiosulphate given intravenously in 0.5-g. doses once or twice daily is of doubtful value. Calcium gluconate and vitamin C may influence capillary permeability. Adrenaline is of doubtful value. Drugs for the purpose of detoxicating the organic arsenicals—the experimental work on which was reviewed in an editorial in the *Journal* (1943, 2, 681)—have not been used by us, but to be of value they would have to be employed early in the disease process. This is not always feasible, since many of the patients are first seen after coma has developed; but the method might have been applied with advantage to our Case 3.

Complications.—Pulmonary oedema is largely avoided by posture. *Hyperpyrexia* is anticipated by routine rectal temperatures and dealt with by tepid sponging and fanning. *Convulsions and restlessness* should receive ruthless treatment. For fits, hexobarbitone sodium followed by paraldehyde by mouth, or sodium phenobarbitone 6 gr. intramuscularly, is indicated. It cannot be stressed too strongly that patients should not be allowed to have fits, because they raise the cerebral capillary pressure in capillaries whose endothelium has already been damaged. *Adequate antimalarial therapy* should be given, as outlined in the "Blue Book" for pernicious cases.

Summary of Treatment.—(1) Examination of the patient. (2) Lumbar puncture. (3) Sit the patient up on a back-rest. (4) Treatment of complications—e.g., pulmonary oedema, fits, hyperpyrexia, etc. (5) Adequate antimalarial therapy. (6) Calcium or sodium thiosulphate i.v., 0.5 g., with calcium gluconate and vitamin C if available (of doubtful value). (7) Adequate hydration and nutrition by transnasal intragastric Ryle tube left *in situ*.

Case Notes

Case 1.—An Indian sepoy, aged 25, was admitted to hospital on the evening of March 31, 1944, deeply unconscious: 1½ hours before admission he had felt giddy and had fallen down unconscious, bringing up blood-stained frothy sputum. On March 5 he had a sore on the penis, and dark-field examination showed *T. pallidum*. Treatment had consisted of three injections of N.A.B. and bismuth, the last injection having been given on March 27. On admission he was in deep coma, responding only to painful stimuli, with stertorous breathing and frothing at the mouth (not blood-stained). The eyes were half opened, with a vacant stare. The general attitude was that of midbrain posture, arms adducted and flexed across the trunk, elbows and wrists flexed and supinated, fingers semiflexed, and lower extremities extended at all joints. There were tonic spasms lasting two to three minutes, associated with stertor, trismus,

some opisthotonos, ocular deviation to the right, and an accentuation of the position, described above. During the resting phase, of similar duration, the arms were often extended and athetoid movements of the fingers were present. A sucking reflex was also elicited at this stage. Just before the height of the tonic phase, flexion of the head to one side produced relaxation of the contralateral limb (Magnus and de Kleijn reflex). Grasp reflex absent; deep reflexes all present and exaggerated; ankle clonus present; plantars extensor and abdominals abolished. Muscle tone appeared normal, as did crude position sense. Conjunctival and pupillary reflexes and swallowing reflex present. C.S.F.: Cells less than 10/c.mm.; proteins, 60 mg./100 c.cm.; chlorides, 720 mg./100 c.cm.; sugar, normal; pressure, no increase. W.B.C., 11,600/c.mm.—polymorphs 54%, lymphocytes 44%, monocytes 2%. Treatment was as described above. April 1: Still in deep coma; urinary incontinence; temperature rose in the evening to 104° F. April 2: Coma lighter; patient easily roused by questioning; plantar reflexes became flexor. April 3: Conscious; B.P. 136/74; still incontinent. April 4: No incontinence. Recovery uneventful.

Case 2.—A Sikh, aged 19, was admitted to hospital on April 15, 1944, deeply unconscious. Five days previously he had received the third injection of N.A.B. for sero-positive syphilis. He was very restless on admission, but when still, lay on his back in a position similar to that of Case 1. There was increased tone in all the limbs, with a tendency to spasmodic arching of the trunk, when the neck became rigid. During the intervals between the spasms the neck was so relaxed as to enable the chin to touch the chest wall. Kernig's sign was negative. Superficial reflexes all present; abdominals brisk; deep reflexes exaggerated and equal on both sides. Spontaneous jaw clonus; no ankle clonus; plantars flexor. Pupils slightly dilated and eccentric; reaction to light sluggish. No facial paralysis. Respirations regular, rapid, rattling. No cyanosis. No engorgement of veins. Skin: secondary rash present. Healed scar on penis. Pulse 140/min.; B.P. 139/70; rectal temperature 103.2° F. Following treatment he became conscious 42 hours after admission. For the next few days his cerebation was slow but speech was unaffected. Improvement was rapid, and he was discharged for further convalescence on May 5.

Case 3.—A Tamil pioneer, aged 20, was admitted to the V.D. ward on June 6, 1944, suffering from balanitis and penile sores. Two days later dark-field examination revealed *T. pallidum*. Anti-syphilitic treatment was given as follows:

June 15: N.A.B., 0.3 g.; bismuth, 0.1 g.
 „ 19: N.A.B., 0.3 g.; bismuth, 0.2 g.
 „ 22: N.A.B., 0.45 g.
 „ 26: Bismuth, 0.2 g.

On June 26 he complained of headache and had slight fever, so no arsenic was given. A blood film showed no malaria parasites. He made no complaint in the evening, and remained well during the next day, although his temperature in the evening rose to 99.4° F. On June 28 he was well early in the morning, but at 11 a.m. suddenly developed a rigor with twitching, and by midday was in deep coma, responding only to noxa. Temperature 102° F.; pulse 144/min.; respirations 18/min. Pupils were dilated, reacting sluggishly to light. No neck rigidity. Deep reflexes all present but sluggish. Conjunctival, abdominal, and cremasteric reflexes abolished. Plantars indefinite. Heart, lungs, and abdomen: N.A.D. No fullness of neck veins. Urine normal. C.S.F.: Pressure, 135 mm. of water; clear; cells 4/c.mm.; protein, 40 mg./100 c.cm.; chlorides, 750 mg./100 c.cm.; sugar, normal. Treatment on the lines described was started, and on the following morning the patient was drowsy, but responded to touch and to questioning. On June 30 he was fully conscious, and thereafter recovery was uneventful.

Case 4.—A Tamil pioneer, aged 22, was admitted to hospital on June 16, 1944, at 11.00 hours, unconscious and having fits. His history was that he had suddenly become unconscious at 10.00 hours. On June 2 sores appeared on the penis. Dark-field examination showed *T. pallidum*, and treatment, with N.A.B., was as follows: June 5, 0.3 g.; June 8, 0.3 g.; June 12, 0.45 g. Temperature on admission was 99.2° F.; pulse 96/min.; respirations 24/min. The patient was lying on his back with his lower extremities extended, and frequently rolled over on his side with his legs drawn up. His arms were moving about in front as if he was trying to grasp some object. Pupils dilated, equal, and reacted sluggishly to light. Consensual reflexes present. There was photophobia. Deep reflexes present; abdominals lost; plantars extensor; and ankle clonus present. Nothing abnormal in heart, lungs, and abdomen. C.S.F.: Pressure, 120 mm. of water; clear; cells less than 10/c.mm.; protein, 300 mg./100 c.cm.; chlorides, 600 mg./100 c.cm. Urine, normal. W.B.C., 8,000/c.mm.—polymorphs 77%, lymphocytes 21%, monocytes 2%. Treatment was given on the above lines, and on the morning of June 17 he was still deeply comatose, responding only to painful stimuli, though the depth of coma lightened towards midday. On the 18th the depth of coma was variable, and the patient became fully conscious the next day. Temperature became normal on June 21, and thereafter the patient remained well, without nervous residua.

Case 5.—A Central Provinces pioneer, aged 18, was transferred from the V.D. Dept. on Sept. 1, 1944. He was a case of sero-positive syphilis, and had received treatment as follows:

Aug. 19: N.A.B., 0.3 g.; bismuth, 0.1 g.
 „ 21: N.A.B., 0.15 g.; bismuth, 0.2 g.
 „ 24: N.A.B., 0.3 g.
 „ 28: N.A.B., 0.15 g.; bismuth, 0.2 g.
 „ 31: N.A.B., 0.15 g.

On transfer the patient was in coma, with the eyes wide open and face congested. There were spontaneous movements of both upper limbs. No neck rigidity. Pupils were equal, central, and reacting to light. Fundus examination showed blurring of the disks, more marked on the left, with congestion of the veins. Deep reflexes present; superficial reflexes absent; ankle clonus present; plantars flexor. There was a macular rash all over the body. Temperature 101.8° F. Heart, lungs, and abdomen: N.A.D. C.S.F.: Pressure, 70 mm. of water; fluid clear; chemically normal. W.B.C., 5,600/c.mm.—polymorphs 75%, lymphocytes 24%, monocytes nil, eosinophils 1%. Treatment was given as in the previous cases, and on the following day (Sept. 2) he was still in coma. Plantars indefinite. In the evening the patient became irritable and resented examination. The plantars became extensor. On Sept. 3 he was conscious but dazed. He answered to his name, but still resented examination. Plantars flexor. On Sept. 4 the patient was fully conscious, and thereafter convalescence proceeded normally.

Discussion

In view of the fact that once capillaries are damaged exudation into the surrounding brain substance is likely to occur, earlier writers (Lees, 1937; Harrison, 1937) have advocated venesection (to reduce congestion), dehydration with hypertonic saline solutions, and lumbar puncture. Cerebral oedema undoubtedly does occur, and is of the interstitial type accompanying head injuries; it is not necessarily associated with a raised intracranial pressure, provided there is free cerebrospinal-fluid absorption. This type of oedema occurs in cerebral contusion and malarial and other encephalopathies.

Cobb (1936) has clearly outlined the physiological mechanism of the cerebral circulation, and notes the following points:

Hydrostatic Factor.—"There is a falling gradient of pressure from artery to vein, steepest in that part of the curve which represents the arteriole. Changes in arterial pressure have very little immediate and direct effect upon capillary and venous pressure, whereas changes in venous pressure affect capillary pressure immediately and conspicuously; in fact, venous and capillary pressures change equally and synchronously."

Osmotic Factor.—"The capillary wall, being a semipermeable membrane... is permeable to all the important osmotically active dissolved substances of the blood except protein, so normally plasma protein tends to prevent movement of fluid out of the vessels. In the arterial capillary bed the hydrostatic pressure is greater than the opposing osmotic pressure of the plasma proteins. Therefore a protein-free fluid is filtered into the tissue spaces. On the venous side of the capillary bed, moreover, the hydrostatic pressure is less than the osmotic pressure of the plasma proteins, and the fluid is reabsorbed. . . . Any obstruction to venous flow, however, will raise the venous and capillary pressure to levels well above the osmotic pressure of the plasma proteins. Filtration from the plasma to tissue spaces will now take place throughout the capillary bed, whereas no real absorption into capillaries is possible; oedema results."

Effects of Posture.—(1) In the horizontal position the venous pressure measures 8 to 15 cm. of water. In the sitting position the cerebral venous pressure becomes negative to atmospheric pressure. (2) In the horizontal position the C.S.F. pressure is roughly equal throughout the ventriculo-subarachnoid system (100 to 160 mm. of water). In the sitting position the intracranial pressure becomes negative to atmospheric pressure, while the pressure in the lumbar sac nearly doubles.

The following table is an attempt to show what we conceive will happen on sitting the patient up; theoretically, the sitting posture should tend to prevent the onset of cerebral oedema (cf., elevation of a traumatized limb to prevent swelling).

Posture	Osmotic Pressure of the Plasma Proteins (mm. Hg)	Venous Capillary Pressure (mm. Hg)	Mean Reabsorption Pressure (mm. Hg)
Horizontal ..	25	12	13
Sitting ..	25	Approximates nil	Approximates 25

Finally, in presenting these cases as arsenical encephalopathy, the criticism may be levelled that they were in reality cases of cerebral malaria. That such may be so cannot be entirely

refuted, since we have seen in the past undoubted cases of cerebral malaria with negative blood slides but with positive brain smears.

However, that five should have occurred is more than a coincidence, and we believe these to have been of arsenical origin rather than malarial. It is most unusual, with three-hourly thick blood films and an expert microscopist, to fail to demonstrate parasites in a true cerebral malaria.

The value of the sitting posture in nursing these coma cases is in no way diminished, since this is the method applied by us with success in the treatment of malarial coma and of the coma of heat-stroke, and we hope that others will apply it to arsenical encephalopathy occurring in an area where malaria is not hyperendemic.

Summary

A brief description of arsenical encephalopathy is given and five cases are described.

That these five patients survived is attributed to the procedure of nursing cases in the sitting position.

The method of treatment is described and the physiology of the procedure discussed.

We wish to express our thanks to Col. F. R. Cawthorn, I.A.M.C., who, having early appreciated the value of a "team," kept its members together despite many difficulties; and to Major R. I. Krishnaswami, I.A.M.C., for help and criticism in the preparation of the paper. Our thanks are also due to the nursing officers, Miss D. J. Oliver and Miss J. St. John Inman, whose untiring efforts have contributed in no small measure to the successful treatment of these cases.

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PROLAPSE OF THE RECTUM IN WOMEN*

BY THE LATE

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Apparently it is not generally realized that prolapse of the rectum in women can be treated successfully by an abdominal operation. Nevertheless this is so, and I hope the following account will demonstrate that the method here described should be included in the armamentarium of those surgeons who have to decide the treatment of patients unfortunate enough to suffer from this distressing complaint.

The operation is one that should not be difficult in the hands of those who are accustomed to operate low down in the pelvis, and its guiding principle is self-evident. The desirability of "hooking it up from inside" must have occurred to surgeons, but I acknowledge my indebtedness to Victor Bonney—to whom, incidentally, gynaecological surgeons owe so much—for information as to whether this was or was not a practical proposition. In his book on operative gynaecology he has given a brief account of such an operation, and this can be consulted with advantage by those sufficiently interested.

A war widow aged 29 consulted me on the advice of a colleague of mine because of a prolapse that had occurred shortly after the birth of her first child, which had taken place five years previously. On examination I found that the prolapse was rectal and that some 4½ to 5 inches of bowel protruded. The tone of the anal sphincters was noticeably weak, and pelvic examination showed that the uterus

* The manuscript of this paper was received from the author on the day before he died.