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ARSENICAL ENCEPHALOPATHY

A REVIEW OF THE LITERATURE WITH A REPORT OF A FURTHER 187 CASES

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(Continued from page 101 of September number)

A series of 187 hitherto unpublished cases of arsenical encephalopathy occurring in India

Clinical material.—All the patients in this large series of cases were members of the armed Forces, who were treated for syphilis as in-patients in hospitals; consequently in every case the onset of symptoms occurred whilst they were under the close observation of medical officers. It was our practice to treat all cases of syphilis in special venereal diseases wards of general hospitals under the care of venereologists and of a trained staff of orderlies, the patient remaining in hospital until the syphilitic lesions were completely healed, when he was discharged to attend for further treatment as an out-patient. As a result of this policy, all the patients in the series were seen and treated by venereologists from the onset of symptoms, with the assistance of the medical specialists in the various hospitals concerned.

In civil clinics, on the other hand, it is customary to treat almost all cases of syphilis as out-patients from the commencement of treatment. As a result it seems to be reasonable to suppose that, if encephalopathy develops, this condition may not be observed, and that death, if it ensues, may quite likely be certified as due to cerebral haemorrhage, or that some similarly convenient diagnosis may be made. The medical practitioner who is called upon to deal with the patient is unlikely to be aware that he is undergoing antisyphilitic treatment, and he can hardly be expected to make an accurate diagnosis without this essential information.

TABLE 5—ANALYSIS OF CASES

Stage of syphilis at commencement of treatment	Number of cases in which encephalopathy developed	Number of injections preceding onset	Number of cases in which encephalopathy developed
Seronegative primary ...	41	1	12
Seropositive primary ...	133	2	64
Secondary ...	9	3	62
Latent in first year ...	2	4	41
Late ...	2	5	8
Total ...	187		Total ... 187

For this reason I am inclined to believe that arsenical encephalopathy is much more common than the reports previously published suggest. It is noteworthy that the highest rate of incidence hitherto recorded appears to have been in patients treated by massive arsenotherapy, and it will be appreciated that all these patients are treated in hospital under careful and continuous observation.

During a period of 20 months (August 1943 to March 1945), in India, 187 cases

of arsenical encephalopathy were reported, all occurring in members of the armed Forces. (See Fig. 5.) Of this number only 2 cases occurred in British patients, as compared with 185 in Indian patients. The total number of patients admitted for antisyphilitic treatment during the period under review was 41,160, of whom 36,300 were Indians and 4,860 were British; this gives a combined incidence of 1 in 220 patients, but with a contrasted racial incidence of 1 in 196 Indian patients and 1 in 2,430 British patients. Of the 187 patients, 60 recovered and 127 (67.9 per cent) died. The incidence of fatal cases was as follows: combined, 1 : 324; for Indians, 1 : 290; for British, 1 : 2,430 patients.

The interval in days between the onset of symptoms and the first injection is shown in Table 6. In approximately half the number of cases injections were given once weekly, the dosage for Indians being usually 0.45 gramme of neoarsphenamine and for British 0.6 gramme; in the remaining cases injections were given twice weekly, and the dosage for Indians was usually 0.3 gramme of neoarsphenamine and for British alternately 0.3 and 0.45 gramme.

TABLE 6—ONSET OF ENCEPHALOPATHY IN 187 CASES

Number of days after first injection	Number of Cases of encephalopathy	Number of days after first injection	Number of cases of encephalopathy
1	8	18	6
2	1	19	3
3	1	20	1
7	1	21	1
8	1	22	1
9	3	23	2
10	6	24	1
11	17	27	1
12	27	30	1
13	35	32	1
14	25	37	1
15	23	56	1
16	12	58	1
17	6		
			Total ... 187

From Table 6 it will be seen that a very large proportion (87 per cent) of all cases occurred 9-19 days after the initial injection and that 74 per cent of all cases occurred after 11-16 days. The average age of the patients affected was 24 years, the youngest being 18 and the oldest 50 years of age.

The onset of symptoms may be sudden or gradual; two distinct types are found. There were 149 patients (79.6 per cent) in whom the onset was sudden, with 107 deaths (71.9 per cent) and 42 recoveries; there were 38 patients (20.4 per cent) in whom the onset was gradual, with 20 deaths (52.7 per cent) and 18 recoveries. In the former group coma or convulsions from the commencement have been considered as a sudden onset, and in the latter group various prodromal symptoms, which may or may not lead to coma or convulsions, have been considered as constituting a gradual onset.

Selected case reports from the Indian series

The following 12 case reports have been selected for inclusion as being typical of a large number of cases.

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Case 3. An Indian, aged 23 years, of good physique. Seropositive primary syphilis.

Treatment.—25.6.44 Neoarsphenamine (N.A.B.) 0.3 gramme. Bismuth 0.2 gramme.

28.6.44	„	„	0.45	„	„	0.2	„
2.7.44	„	„	0.3	„	„	0.2	„
5.7.44	„	„	0.45	„	„	0.2	„
9.7.44	„	„	0.3	„	„	0.2	„

On 5.7.44, after the fourth injection, the patient's temperature rose to 102°F, returning to normal within 48 hours. On 9.7.44 the fifth injection was given. Approximately 30 hours later he had a sudden epileptiform fit and became semi-comatose. Photophobia was marked, temperature normal, pulse rate 120 and very feeble. One hour later coma had deepened and there was a right facial paresis with occasional twitching of the muscles on the affected side. The pupils were dilated and the arms and legs spastic, with exaggerated deep reflexes; abdominal reflexes were absent and there was a flexor plantar response. There were marked athetoid movements of the right hand. Seventeen hours later the general condition was deteriorating and the coma deepening; pupil reactions were extremely sluggish. Shortly afterwards there was marked cerebral irritation with restlessness, and 48 hours after the onset there were signs of returning consciousness. The temperature was 100°F., pulse 120, respirations 34; the pupils were smaller and reactions fairly brisk. Three hours later the patient was fully conscious, responding to commands and showing no signs of cerebral irritation. Râles were present at the bases of the lungs. Improvement continued and the patient was discharged from hospital on 6.8.44. The cerebrospinal fluid was not under pressure; it contained 1 lymphocyte per cubic centimetre; globulin was increased, total protein was 120 milligrams per cent, and the fluid was sterile on culture.

Additional treatment.—Sodium thiosulphate intravenously every 4 hours. Adrenaline, 1 cubic centimetre every 4 hours. Repeated lumbar puncture. Oxygen by B.L.B. mask for 5 minutes every half-hour. Rectal saline drip.

After-history.—On account of an error the patient was given a further intravenous injection of neoarsphenamine some time after his recovery, fortunately without ill effects. Treatment was continued with bismuth and later with penicillin.

Case 6. An Indian aged 25 years, of good physique. Seronegative primary syphilis.

Treatment.—21.2.45 Neoarsphenamine (N.A.B.) 0.3 gramme. Bismuth 0.2 gramme.

26.2.45	„	„	0.3	„	„	0.2	„
1.3.45	„	„	0.3	„	„	0.2	„
5.3.45	„	„	0.3	„	„	0.2	„

On 6.3.45, 24 hours after the fourth injection, the patient complained of dizziness and marked irritation of the skin and shortly afterwards fell down. Two hours later he became semi-comatose and was acutely apprehensive and restless, with athetoid movements of both arms. The pupils were dilated and reacted sluggishly to light; corneal reflexes were present. Deep reflexes were exaggerated, abdominal reflexes were absent and there was a flexor plantar response. The coma gradually lessened 24 hours after its onset, but the patient remained acutely apprehensive for a further 4 days, at the end of which time his condition was normal. He was finally discharged from hospital on 15.3.45.

Additional treatment.—Morphia $\frac{1}{4}$ grain, with atropine $\frac{1}{100}$ grain, twice daily. BAL (British anti-lewisite, 2:3-dimercaptopropanol) 1 ampoule four-hourly for 4 doses, followed by 1 ampoule twice daily for a further 3 days. Rectal glucose saline, and later fluids, by mouth.

Case 8. An Indian, aged 24 years, of moderate physique. Seropositive primary syphilis.

Treatment.—15.3.45 Neoarsphenamine (N.A.B.) 0.3 gramme. Bismuth 0.2 gramme.

18.3.45	„	„	0.3	„	„	0.2	„
26.3.45 Penicillin 20,000 units four-hourly until 28.3.45 (18 doses).							

On 28.3.45 at 2.30 p.m., the patient absconded from hospital and was found at 8.30 a.m. on the following day in a dazed condition. He was disorientated and irrational, and at 9.30 a.m. he had an epileptiform attack and became semi-comatose. There was marked apprehension, also acute hyperaesthesia and athetoid movements of the limbs. The pupils were widely dilated but reacted normally to light and in accommodation. Abdominal

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reflexes were absent and deep reflexes exaggerated, and there was a flexor plantar response. Complete recovery took place in 3 days.

Additional treatment.—Morphia as required. BAL 2 cubic centimetres four-hourly for 4 doses.

Case 9. An Indian, aged 20 years, of fairly good physique. Seropositive primary syphilis.

Treatment.—20.2.45. Mapharside 0.03 gramme

24.2.45	,,	0.03	,,
1.3.45	,,	0.03	,,
4.3.45	,,	0.03	,,

On 6.3.45, the patient suddenly had a fit, clonic in type, and immediately became deeply comatose. He was very restless. The pupils were widely dilated and reacted sluggishly to light; corneal reflexes were present. Abdominal reflexes were absent, deep reflexes were exaggerated and there was a flexor plantar response. Blood pressure 158/85. Temperature 101°F. Pulse 98. The condition remained unchanged until 15 hours later, when the temperature was 105°F. and the pulse thready and very rapid. Death occurred 3 hours later, 18 hours after the onset of symptoms.

Additional treatment.—BAL., 2 cubic centimetres every 4 hours, had been given.

Pathological findings.—In the brain there was well marked pericapillary transudation. The perivascular spaces of His were very wide. Capillary endothelium was absent in almost all the finer branches. The periphery of the capillary lumen showed accumulation of small lymphocytes. A few small lymphocytes were also present in the brain tissue in the vicinity of these capillaries.

Case 12. An Indian, aged 20 years, of moderate physique. Seropositive primary syphilis.

Treatment.—25.1.45 Nearsphenamine (N.A.B.) 0.3 gramme. Bismuth 0.2 gramme

1.2.45	,,	0.3	,,	0.2	,,
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On 6.2.45, the patient suddenly began to have convulsive attacks, and coma rapidly supervened. There was twitching of the face, and there were athetoid movements of the upper limbs. The pupils were widely dilated, with sluggish reaction to light; the corneal reflexes were present. Abdominal reflexes were absent and deep reflexes exaggerated, and there was a flexor plantar response. Blood pressure 125/90; temperature 101°F., pulse 120. The condition steadily deteriorated and the patient died 8 hours after commencement of the attack.

Additional treatment.—This had been given as under. Adrenaline every 4 hours. Lumbar puncture: 20 cubic centimetres of fluid withdrawn. Venesection twice (300 and 120 cubic centimetres). Glucose saline, sodium thiosulphate and calcium gluconate, intravenously. Magnesium sulphate rectally. Coramine (nikethamide), morphia and atropine.

Pathological findings.—Brain: meningeal vessels and vessels of choroid plexus markedly engorged, capillaries dilated. Oedema of meninges. Perivascular exudation with round-celled infiltration.

Case 21. An Indian, aged 23 years, of slight build. Seronegative primary syphilis.

Treatment.—12.10.44 Nearsphenamine (Evarsan) 0.15 gramme. Bismuth 0.2 gramme

15.10.44	,,	0.3	,,	0.2	,,
19.10.44	,,	0.3	,,	0.2	,,

On the evening of 19.10.44, the patient's temperature rose to 100.6°F. and he was therefore confined to bed. Three days later he became very apathetic, restless and drowsy, but responded to questioning. Later he became apprehensive, noisy and extremely restless, with a gradual onset of coma. Pupils widely dilated, no reaction to light; corneal reflexes absent; deep reflexes exaggerated; abdominal reflexes absent; plantar response flexor. Coma gradually deepened and the patient died 30 hours after the onset of symptoms.

Additional treatment.—He had been nursed in Fowler's position. Venesection, 1 pint; lumbar puncture, 30 cubic centimetres withdrawn; sodium thiosulphate intravenously; adrenaline.

Pathological findings.—Brain: sections from various parts of the brain (cortex, basal ganglia, pons) showed intense congestion and oedema. There were large extravasations of erythrocytes into the perivascular spaces and slight perivascular "cuffing" with round cells. Many of the capillaries showed partial thrombosis. The capillary endothelium was swollen. In the cortex and basal ganglia (nuclei) these changes were marked.

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Case 24. An Indian, aged 24 years, of moderate physique. Seropositive primary syphilis.

<i>Treatment.</i> —	6.12.44	Neoarsphenamine (Evarsan)	0.225 gramme.	Bismuth	0.2 gramme	
	10.12.44	"	"	0.3	"	0.2 "
	13.12.44	"	"	0.225	"	0.2 "
	17.12.44	"	"	0.3	"	0.2 "
	20.12.44	"	"	0.225	"	0.2 "

On 30.12.44, the patient had a rigor followed by slight fever, with temperature 100.5°F. which returned to normal within 24 hours. For the next few days he complained of a headache, severe at times. At 9.30 a.m. on 5.1.45, fever, headache and drowsiness developed. By 11 a.m. on the same day he was semi-comatose, delirious and very restless. His temperature was 101°F. and his pulse rate 80. The pupils were normal and reacted to light; corneal reflexes were present, abdominal reflexes absent, deep reflexes exaggerated, plantar response flexor. On the following morning he fully recovered consciousness and made an uninterrupted recovery.

Additional treatment.—Morphia as required; adrenaline every 4 hours; glucose saline intravenously.

Case 42. An Indian, aged 25 years, of good physique. Seropositive primary syphilis.

<i>Treatment.</i> —	9.8.44	Neoarsphenamine (Neokharsivan)	0.3 gramme.	Bismuth	0.2 gramme	
	13.8.44	"	"	0.45	"	0.2 "
	16.8.44	"	"	0.3	"	0.2 "
	22.8.44	"	"	0.45	"	0.2 "

Seven hours after the last injection the patient had a sudden fit and fell out of bed. He was unconscious and there were violent movements of all limbs. Shortly afterwards he regained consciousness, but was mentally confused although able to obey orders. A second fit occurred one hour later, accompanied by less violent movements of the limbs. He rapidly lost consciousness. He was restless, with breathing slightly stertorous and eyes turned upwards. There were athetoid movements of the upper limbs, sustained for about one minute and punctuated by akinetic periods of about $\frac{1}{2}$ minute, when one or other upper limb usually curled around the pillow or the back of the neck. There were asynchronous irregular flexion movements of the lower limbs, executed singly and involving one or other knee or hip joint. Pupils were equal, moderately dilated, corneal reflexes active. All deep reflexes were exaggerated, abdominal reflexes absent; plantar response was flexor, sensibility to pain retained. Cerebrospinal fluid was clear and colourless and not under pressure. Coma gradually deepened, movements ceased and temperature rose steadily from 101°F. until it reached 109.2°F., when death occurred 24 hours after the onset of symptoms.

Pathological findings.—Brain: surface deeply injected, numerous small haemorrhages in the white matter, cortex and basal nuclei. No frank haemorrhage over the surface of the brain. The meninges were delicate and the large meningeal vessels, veins and arteries congested, one meningeal vein being thrombosed. There was some viscous exudation into the perivascular spaces of the smaller arteries and within the meninges. A few small capillary haemorrhages were present. In the medulla, in the region of the abducens nerve, there was a circumscribed subependymal haemorrhage, probably arising from a vein. The large vessels of the white matter showed severe red stasis and early thrombosis, with softening in the region of the thrombosed vessels.

Case 171. An Indian, aged 23 years, of slight build. Seropositive primary syphilis.

<i>Treatment.</i> —	22.1.44	Neoarsphenamine (N.A.B.)	0.3 gramme.	Bismuth	0.2 gramme	
	29.1.44	"	"	0.3	"	0.2 "

At 10 p.m. on 3.2.44, when the patient was seen, he was apparently well. An hour later he had a fit, and on examination was found to be semi-comatose and did not respond to questions. He was very irritable, with extreme photophobia, trismus, athetoid movements of the limbs and twitching of the face. The pupils were dilated and responded to light. Slight neck rigidity but no rigidity of the limbs. Deep reflexes brisk, abdominal reflexes absent, plantar response flexor. Vomited twice. Lumbar puncture displayed clear fluid with no increase in pressure. At 11.30 a.m. on the following day the patient was semi-comatose and resisted forcible opening of the eyes. The teeth were tightly clenched and he swallowed with difficulty. Occasional slight twitching of the fingers and facial muscles.

No convulsions; arms and legs held rather rigidly. Purpuric spots over right shoulder; haemorrhages into right upper and lower eyelids and left lower eyelid. At 6 p.m. he had clonic convulsions lasting for a few minutes. On the morning of 5.2.44, the patient was more conscious of his surroundings, opened his eyes and looked around, but did not speak. Trismus still present. Incontinence of urine. There was slow improvement during the day and by the next day he was able to speak. During the early hours of 7.2.44, he had another fit with clonic convulsions and again became semi-comatose. Towards evening he was much more rational and was able to speak, but he could not carry out purposive movements. During the night he had hallucinations, which occurred again on the two following nights, when he complained of hawks flying around his bed. Progress from then on was steady, and on 14.2.44 he was able to remember past events and to sit up and take food. From this time onwards he made an uneventful recovery, but he was mentally rather confused for several weeks, at the end of which time he was discharged to convalescence (10.3.44).

Additional treatment.—Repeated lumbar puncture. Sodium thiosulphate intravenously; adrenaline; glucose intravenously; fluids.

Case 172. An Indian, aged 23 years, of slight build. Seronegative primary syphilis.

Treatment.—21.10.43 Sulpharsphenamine (Sulphostab) 0.3 gramme. Bismuth 0.2 gramme

24.10.43	Neoarsphenamine (N.A.B.)	0.45	„	„	0.2	„
31.10.43	„	0.45	„	„	0.2	„

The first injection was given intramuscularly, the second and third intravenously.

On 3.11.43 the sore was healed. The patient was apparently well until about 10 p.m. when he began to have convulsions. This was not reported, and he was not seen by a medical officer until 8 o'clock the following morning, by which time he was in coma, having severe clonic contractions of the whole body. Pulse weak and rapid; respiration rapid and shallow. Temperature 104°F. Neck rigidity present, photophobia marked, pupils dilated but reacting to light. Constant twitching of face and jaw muscles. Lumbar puncture showed a clear fluid under slight pressure. Convulsions continued and became more severe during the day. Death occurred at 7 p.m.

Additional treatment.—This had consisted of repeated lumbar puncture, adrenaline four-hourly and intravenous glucose.

Pathological findings.—Brain: considerable congestion of all cortical blood vessels; no subarachnoid haemorrhage; no emboli found and no haemorrhage in the brain substance.

Case 173. An Indian, aged 30 years, of good physique. Seronegative primary syphilis.

Treatment.—24.8.43 Neoarsphenamine (N.A.B.) 0.3 gramme. Bismuth 0.2 gramme

30.8.43	„	0.45	„	„	0.2	„
6.9.43	„	0.45	„	„	0.2	„

At 6 p.m. on 10.9.43, whilst playing cards, the patient suddenly got up, complaining of a headache, and lay down on his bed. His face and hands began to twitch and he did not answer when spoken to. On examination the patient was found to be unconscious and very irritable, with extreme photophobia and muscular twitchings of face and hands. He was restless and plucking at the bedclothes. Temperature 101°F. pulse 112; blood pressure 130/85. Neck rigidity but no Kernig's sign. The upper limbs were not rigid but had marked athetoid movements. Deep reflexes were exaggerated, abdominal reflexes absent; plantar response was flexor. Lumbar puncture showed clear fluid under slight pressure. At 6 a.m. on the following day the temperature rose to 104°F. and the patient was still very restless and irritable. Photophobia and twitching as before, patient still comatose. Respiration rapid and sometimes stertorous. Some clonic convulsions of the body. During the next day the temperature gradually fell, to reach 100°F. towards evening. Coma was still present but patient much quieter with no convulsions. On 13.9.43 the temperature was normal and the patient quiet with signs of returning consciousness but disoriented. By the following day he was fully conscious and able to take fluids. Progress was uninterrupted from this time onwards, but he remained rather dazed and complained of headaches for 2-3 weeks. He was finally discharged from hospital on 6.11.43.

Additional treatment.—Repeated lumbar puncture; adrenaline glucose intravenously.

Case 174. An Indian, aged 18 years, of slim build. Seropositive primary syphilis.

Treatment.—31.8.43 Neoarsphenamine (N.A.B.) 0.3 gramme. Bismuth 0.2 gramme

6.9.43	„	0.45	„	„	0.2	„
12.9.43	„	0.45	„	„	0.2	„

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At 6 p.m. on 17.9.43, the patient suddenly had a convulsion and rapidly became unconscious. On examination he was found to be semi-comatose and did not answer questions; he was very irritable, with extreme photophobia and slight neck rigidity. Kernig's sign absent. Temperature 104.4°F; respiration normal; pulse 70. Pupils normal, reacting to light. Deep reflexes exaggerated, abdominal reflexes absent; athetoid movements of upper limbs. Lumbar puncture displayed slight increase in pressure, clear fluid and slight increase in protein. On the following day the temperature was 101°F. There was little change in the general condition. The patient was still semi-comatose but quiet. On 19.9.43 his general condition had improved and he was able to take fluids, although he vomited twice. On 20.9.43 he was fully conscious and taking fluids well. On 20.9.43 he was feeling well and mentally alert. From this time onwards he made an uninterrupted recovery; he was discharged from hospital on 26.10.43.

Case 3 is of particular interest, in that the patient was given a further injection of neoarsphenamine, after his recovery from encephalopathy, without any untoward effects.

Analysis of symptoms and signs in 187 cases

From a close study of the case histories of all patients, the following appear to be the more common symptoms and physical signs of arsenical encephalopathy.

Cases with gradual onset

Symptoms.—These include feeling vaguely unwell, apprehension, anorexia, apathy, drowsiness, confusion, answering questions slowly and vaguely, wandering aimlessly about, rowdiness, restlessness, incoherence, disorientation, headache, vomiting, gradual onset of convulsions and coma.

Clinical signs.—These include fever (usually 101°F. tending to rise), marked hyperaesthesia in many cases, dilated pupils which may or may not react to light. Corneal reflexes are present, abdominal reflexes almost always absent, deep reflexes increased; plantar responses are flexor. Athetoid movements, chiefly in the upper limbs, are a very constant sign, as are twitching of the facial muscles and rigidity of the neck. Kernig's sign is not present. Incontinence of urine is common.

Cases with sudden onset

The first indication was either violent convulsive fits with a very rapid onset of coma, or sudden and deep coma without fits. The clinical signs were as above.

Pathology in the Indian series

It was not possible in all cases to undertake a detailed pathological examination, but the brain was closely examined in at least 40 cases and I am indebted to Major Krainer for the following general description.

One subject only showed extensive hæmorrhages and may be considered a typical hæmorrhagic encephalopathy. One subject showed perivascular demyelination; in that case death had occurred 72 hours after the onset of coma. The other subjects showed congestion, scanty hæmorrhages (mainly perivascular), some round-celled infiltration (chiefly in the basilar portion of the pons), and viscous exudation without hæmorrhage in the perivascular spaces. Oedema of the brain was not conspicuous.

Nomenclature of arsenical encephalopathy

A great variety of names have been given to this condition. These have been discussed by Alpers, who believes that the term, hæmorrhagic encephalitis, is a poor one, because hæmorrhage is not an important part of the process and is not inflammatory, thus the adjective is contradictory to the implication of the noun, encephalitis. "Brain purpura" is also inadequate, because the pathology is not a purpura but merely a purpuric rash. "Serous apoplexy" is not a good term, because it does not explain the picture in all cases. Alpers suggests the term, medullary perivascular necrosis. Globus and Ginsburg suggest the name, pericapillary encephalorrhagia, whereas Scheinker believes that "encephalopathy due to arsenic" is the best description, because it indicates that the pathological process is not an inflammatory one and, at the same time, it covers the vascular,

haemorrhagic and non-haemorrhagic alterations of the tissue. Throughout this article use is made of the term, arsenical encephalopathy, which appears to be the most satisfactory one.

Causation of encephalopathy in the Indian series

It has not been possible to arrive at any satisfactory conclusion as to the causation of this serious complication of arsenotherapy. I am inclined to the view that individual idiosyncrasy is a possible but unsatisfactory explanation. Sensitivity to the arsenical compound is not a probable cause, as cases have been reported in which a further dose of arsenic has been given after recovery, as is shown in Case 3 of this series. Toxicity of the compound can be excluded with certainty; in every case a sample of the same batch of the compound has been carefully examined and in no case was a toxic sample found. Furthermore, in one instance the contents of an ampoule of 0.9 gramme neoarsphenamine were given to two patients, in one of whom encephalopathy developed whereas the other was unaffected; this observation confirms the experience of other authors quoted above. It is well known that a solution of the arsenical compound rapidly becomes toxic on exposure to the air, but there is no reason to suppose that this happened in the cases concerned, seeing that careful instructions were issued, prior to the occurrence of encephalopathy, regarding the dangers of carelessness in this matter.

As stated above, it is not considered that the dosage plays any important part, since cases have occurred after so small a dose as 0.15 gramme of the arsenical compound. Again, for reasons given above, I cannot support the theory that encephalopathy is a Herxheimer reaction. Furthermore, it is of interest to note that, whereas a Herxheimer reaction is common after treatment with penicillin, encephalopathy after penicillin treatment is unknown.

Chronic arterial disease as a possible cause can be ruled out entirely. All the patients were young men, mostly between 20 and 30 years of age, who had been medically examined before joining the Army. It is not known what part, if any, is played by hepatic or adrenal insufficiency, because no tests of these functions were made in my cases; it was equally impossible to investigate the colloidal equilibrium of the blood. The pathological findings would seem to support a direct toxic action on the brain capillaries; the work undertaken by D. Black on the arsenic content of the brain is also significant.

Reference is made above to the fact that Cole and his colleagues found the condition to be less common in the Negro than in white patients. Our experience with Indian patients was directly opposed to this: the incidence in coloured patients was 1:196, compared with 1:2,430 in white patients. It was suggested that South Indians were more susceptible than were those from the north, but a careful study of the complete records does not support this view. On account of temporary difficulties of supply and transport, it was not always possible to use the same manufacturer's compound on each occasion, but although a number of patients were given different compounds on separate occasions, the vast majority received the same one each time. This, therefore, does not appear to be of any particular significance.

It is, however, of great significance that 74 per cent of cases occurred 11-16 days after the first injection—a time interval commonly associated with anaphylactoid reactions from other causes. It is true that a number of cases (12 in all) did occur after the first injection, but one is always faced with the possibility that the patient in India has consulted a local practitioner, who may have given an injection, before the patient reported his illness to the military authorities. It is suggested that anaphylaxis cannot be ruled out as a possible cause. The theory, that if the cerebrospinal fluid reaction is positive before commencement of treatment arsenical encephalopathy is more liable to develop, is discussed above; the evidence produced does not appear to be of statistical value.

Treatment of arsenical encephalopathy

Various forms of treatment have been used in our own and other cases, but

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none appears to have any important effect. I do not consider that sodium thio-sulphate is of any value whatsoever. In view of the fact that the cerebrospinal fluid is rarely under pressure, repeated lumbar puncture (although performed in our cases) does not appear to be necessary or justifiable. Venesection may be of some value. Glucose saline is of value and should be given by the method of continuous drip. Adrenaline may be given four-hourly.

Parnell and Dudley suggest anoxaemia as a possible causal factor and Byrne believes the condition to be the result of interference with tissue respiration. He suggests oxygen, given with a B.L.B. mask, and the injection of 10 cubic centimetres of a 10 per cent aqueous solution of methylene blue intravenously, thrice daily, to act as an oxygen transporter and possibly to counteract the oxidation of glutathione by arsenic.

In view of the fact that vitamin B₁ deprivation may be a possible factor, it is suggested that this substance be given before treatment is begun. Certainly it would be important to estimate the vitamin B₁ content of the blood and urine in these patients, and in the case of Indians the pyruvic acid level should also be investigated. Fortunately, before it was possible to arrange for these investigations, all cases of encephalopathy ceased because of the substitution of penicillin for arsenic in the treatment of syphilis.

The substance, BAL, was used in a number of cases but appeared to have little influence on the condition. Morphia is most valuable in controlling the convulsions and should not be withheld. In view of the fact that bronchopneumonia frequently supervenes, it was considered to be important to nurse patients who were comatose in the Fowler's position; the advantage of this has been borne out by Ransome, Paterson and Gupta.

A point of diagnostic importance is mentioned by Curtis, who stresses the value of the positive pressure tourniquet test (Rumpel-Leede phenomenon). He had applied this test to 7 of his patients in whom encephalopathy subsequently developed; all (with one exception) had a positive reaction before the onset of symptoms. It is of historical interest to note that Ehrlich recommended trephining of the skull as a method of treatment. No evidence that it has been performed, however, exists in the literature, and no instance of recovery following such an operation has been recorded.

Summary and conclusions

- (1) An extensive survey of the literature has been made.
- (2) A series of 187 cases of encephalopathy which occurred in India are reported and discussed.
- (3) The condition is not so rare as has been supposed. Indians are particularly susceptible to it.
- (4) Individual idiosyncrasy and anaphylaxis are believed to be important factors in its causation.
- (5) Treatment is unsatisfactory. The most useful remedies are morphia, adrenaline and glucose saline. Vitamin B₁ and oxygen are suggested as being of value. Nursing in Fowler's position is recommended.

In conclusion, I wish to thank all the venereologists who, by keeping such careful records, have enabled me to compile this paper; it is quite impossible to mention them all by name. I must, however, mention, Lieutenant-Colonels J. Eapen, N. V. Rao, and S. C. Banerjee and Captain T. D. Carson in the Army in India. I am indebted to a number of pathologists for the pathological details and to various medical specialists for their help in the treatment of these patients, especially to Lieutenant-Colonel R. J. McGill. The help given by Major L. Krainer (neuro-pathologist) and Major D. Black (biochemist) is acknowledged in the text. Finally I wish to thank Dr. A. O. F. Ross for his helpful suggestions in the preparation of this article.

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VENEREAL DISEASES IN THE ARMED FORCES OVERSEAS (1)*

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This is an opportunity, perhaps belated, to recount my experiences whilst serving as Adviser (and later Consultant) in Venereal Diseases to the Middle East Forces and then to the Central Mediterranean Forces. In May 1940, when I was distinctly bored with an army life at Woolwich which meant about three hours' work a day, an unexpected order came that I was to prepare for service in the Middle East as "Adviser in Venereology". My preparation consisted mainly of over two months' idleness in a tent on Aintree racecourse—but such is the way of the Army !

The long sea voyage was broken by three days in Capetown, and no praise is too high for the kindness and hospitality of the people of South Africa. At last, after many more weeks of heat and boredom, we reached Suez, where commenced a long and intimate acquaintance, not always pleasant, with Egyptian railways. I vaguely remember that a journey which normally takes three hours by road occupied over seven hours in stifling heat and ended in the dark, on an empty railway siding, miles outside Cairo. Even the longest journey, however, has an end, and in our hotel the same night we decided, after a bath and a very long iced drink, that the life was not going to be too bad.

This was the first and longest of many journeys—some very pleasant, others

* An address to the Medical Society for the Study of Venereal Diseases, 25th May 1946.