reason for this apparent selection is obscure, and our observations throw no new light on this aspect. From the study of the four cases reported one interesting feature emerges—namely, the interval between the first injection and the onset of the condition. It is not without significance that in three of them haemorrhagic encephalitis occurred about the tenth day after beginning treatment—a time when it is not uncommon to find other signs of intolerance to arsenic in the syphilitic patient. Indeed, one of our patients did manifest a concomitant morbilliform rash. Haemorrhagic encephalitis does occur in patients receiving arsenical therapy for non-syphilitic nervous disorders, but not with the same characteristic time interval. Therefore one may assume the syphilitic infection itself cannot be excluded as a factor in the aetiology.

Finally, two extraneous factors may be mentioned. It will be noted that these four cases occurred in winter-time, when as a general rule vitamin intake is at its lowest, especially vitamin C. Also they have been reported since the onset of the war. Conditions in wartime naturally impose greater mental stress and strain on the individual, and more so on the patient with syphilis.

Conclusion

Haemorrhagic encephalitis is a rare complication of treatment with arsenic in syphilis.

It is impossible to determine in advance the type of individual who will develop this complication, but the pregnant woman with syphilis should be regarded as a "potential reactor."

The clinical signs are those of cerebral irritation, and may be preceded by such symptoms as headache and dizziness.

The condition is rapidly fatal unless diagnosis is prompt and treatment immediate.

We wish to thank Dr. Ross and Dr. Sanderson for kindly allowing us access to their case.

BIBLIOGRAPHY

- Alpers, B. J. (1928). *Arch. Neurol. Psychiat.*, Chicago, **20**, 497.
 Dickens, P. F. (1928). *U.S. Nav. med. Bull.*, **26**, 192.
 Friedman, C. F., and Shinefeld, M. A. (1941). *Amer. J. Syph. Gon. V.D.*, **25**, 610.
 Glaser, M. A., Imerman, C. P., and Imerman, S. W. (1935). *Amer. J. med. Sci.*, **189**, 64.
 Globus, J. H., and Ginsburg, S. W. (1933). *Arch. Neurol. Psychiat.*, Chicago, **3**, 1226.
 Ingraham, N. R., jun. (1939). *J. Amer. med. Ass.*, **112**, 1537.
 Lees, David (1940). *Diagnosis and Treatment of Venereal Diseases*, Edinburgh.
 Netherton, E. W. (1934). *Med. Clin. N. Amer.*, **17**, 1005.
 Paley, S. S., and Pleshette, N. (1939). *Amer. J. Syph. Gon. V.D.*, **23**, 69.
 Parnell, R. J. G., and Dudley, S. F. (1920). *Lancet*, **1**, 190.
 Raiziss, G. W., and Koppelman, A. (1927). *J. Chemother.*, **4**, 7, 55.
 Russell, D. S. (1937). *J. Path. Bact.*, **45**, 357.
 Stokes, J. H. (1934). *Modern Clinical Syphilology*, 2nd ed., Philadelphia.
 — (1939). *Amer. J. Syph. Gon. V.D.*, **23**, 549.

A CASE OF HAEMORRHAGIC ENCEPHALOPATHY FOLLOWING ARSENICAL THERAPY

BY

JAMES P. A. HALCROW, M.B., M.R.C.P.Ed., D.P.H.
 Medical Registrar, E.M.S.

The following case of arsenical encephalopathy is thought worthy of publication in view of the few references to this complication of arsenical therapy in recent British literature, and also because of the increasing incidence of syphilis at the present time.

Cases in the Literature

Serious cerebral complications following treatment with arsenical preparations are fortunately rare. Haemorrhagic encephalopathy or serous apoplexy is a complication of arsenical therapy which usually ensues within two or three days of the second or third injection of an arsenical preparation. The onset is characterized by drowsiness, irritability, and depression, followed by epileptiform convulsions and coma. The prognosis is bad unless cases are recognized early and prompt treatment is instituted. Lees (1937) mentions nine cases, five of which recovered. Winter (1940) describes a case of primary syphilis in a healthy young adult in which symptoms developed two days after the second injection of an arsenical preparation. The early symptoms in Winter's case were slight

nausea, headache, and feverishness. Examination revealed a scarlatiniform rash on the trunk, limbs, palms of the hands, and soles of the feet. The temperature rose to 104° F., the rash became more marked, and oedema of hands and arms developed. Vomiting was a feature, but mental and nervous symptoms were lacking. The rash became purpuric, and about 48 hours from the onset mild mental symptoms developed, followed by loss of consciousness and death. Necropsy revealed oedema of the brain and multiple haemorrhages throughout the brain substance. Friedman and Newman (1941) describe a case of encephalitis in a syphilitic subject aged 28; again the symptoms appeared shortly after a second dose of an arsenical preparation. These symptoms were epileptiform convulsions, projectile vomiting, and rectal and urinary incontinence. Examination revealed no abnormal neurological findings. The cerebrospinal fluid was not under pressure; it contained 15 cells per c.mm. and total protein 70 mg. per 100 c.cm. Their case recovered, after administration of adrenaline intramuscularly and glucose intravenously. Friedman and Shinefeld (1941) describe two cases in syphilitic children, both of whom died. In their cases symptoms occurred after several injections of arsenical preparations. The symptoms were irritability, convulsions, and coma. In one case cerebrospinal-fluid protein was 297 mg. per 100 c.cm. Russell (1937) describes the pathological findings in three cases. She found perivascular and ring haemorrhages, and also perivascular non-haemorrhagic areas of necrosis and demyelination in the central nervous system. All three were serologically positive cases of syphilis in young adults, the eldest being 31 years old. Symptoms in two of her cases appeared shortly after the second injection of an arsenical preparation; in the third case symptoms followed the third injection. All three patients died within four days of onset.

Case Report

Male aged 22. No previous history of ill-health. Treated for acute gonococcal infection from March 4 to 12, 1942, in V.D. hospital, and readmitted to the hospital on April 12 with multiple indurated ulcers on coronal sulcus. *Spirochaeta pallida* present on examination with dark-ground illumination. Treatment consisted of: April 11: novostab 0.45 g., chlorostab 1 c.cm. April 14: neo-kharsivan 0.3 g. April 18: novostab 0.45 g., chlorostab 1 c.cm. On April 21 the patient felt out of sorts, hot, and flushed; temperature 102° F. During the next two days temperature varied from 100° to 102° F. He was depressed, but made no special complaint. At 7 a.m. on April 23 he had an epileptiform convulsion and vomited bile-stained fluid; admitted to E.M.S. hospital.

Examination.—Temperature 98° F., pulse rate 78, respirations 20. Semi-comatose on admission; incontinent, with noisy moaning respirations; colour good. Pupils equal, circular, and contracted: reacted sluggishly to light. No neck rigidity, and Kernig's sign negative. All reflexes were exaggerated and ankle clonus was present; plantar responses doubtful flexor; abdominal reflexes present and normal. Other systems normal. Blood pressure 120/70. **Fundi:** Slight blurring of disk edges right side. Left side normal. **Urine:** S.G. 1030; no abnormal constituents; no red blood cells or casts. White cell count 12,000. Lumbar puncture at 11 a.m.: cerebrospinal fluid not under pressure; fluid contaminated with blood. **Blood:** Wassermann reaction ++, Kahn negative. Flocculation test, 1:16.

A few hours after admission plantar reflexes became extensor and respirations stertorous. By evening temperature had risen to 104° F. Pulse rate 118; respirations 40. Lumbar puncture repeated: cerebrospinal fluid clear; pressure 250 mm. water; cells 5 per c.mm.; Wassermann reaction negative; protein 230 mg. per 100 c.cm. By the following morning coma was deep, with marked venous congestion. Venesection performed and 14 oz. of blood withdrawn. Lumbar puncture repeated—10 c.cm. cerebrospinal fluid removed: pressure 260 mm. water; cells 5 per c.mm.; protein 270 mg. Kahn negative. By 2 p.m. on April 24 coma had deepened; temperature 104.8° F., pulse rate 108, respirations 32. Marked cyanosis, and at 6 p.m. patient had two epileptiform convulsions. Lumbar puncture repeated. Thereafter coma steadily deepened, and after two further epileptiform convulsions the patient died at 3 a.m. on April 25.

Necropsy

Apart from the central nervous system, all organs were normal except for punctate haemorrhages on the upper surface of lower lobe of right lung.

Brain: Macroscopic Appearance.—Considerable congestion of the pia-arachnoid all over the brain, with several irregular haemorrhages—one on the upper surface of the left half of the cerebellum, one on the contiguous lower surface of the corresponding occipital lobe, and

a third at the right temporo-sphenoidal lobe. Small cerebellar cone round the brain-stem. Section of brain revealed congestion of grey matter and small congested vessels in the white matter. After fixation, sections of brain revealed a fair number of petechial haemorrhages, more marked in the white matter. Macroscopically the grey matter of the brain was congested, giving a pinkish hue. Many small congested vessels in white matter.

Microscopical Examination.—The lesions present were not numerous, therefore careful searching was necessary. Some blocks of brain tissue did not reveal any lesion. No particular part of the brain was especially involved, the lesions being irregularly distributed throughout the brain substance. They were perhaps more obvious at the junction of white and grey matter than anywhere else in the cortex. Main lesions in intracerebral vessels, consisting of endothelial swelling associated with ante-mortem thrombi, partially occluding the lumen of the vessels. Some of the thrombi were infiltrated with polymorphonuclear leucocytes, many of them eosinophils. Occasionally there was evidence of vascular rupture, with red blood cells and eosinophilic material in the Virchow-Robin spaces. No obvious change in nerve cells themselves, and there was absence of perivascular cuffing and other signs of encephalitis. Emulsions of the brain were injected into rabbits and mice with negative results.

Treatment

This consisted of repeated lumbar punctures. Adrenaline was given in doses of 1 c.cm. intramuscularly four-hourly, and sodium thio-sulphate was injected intravenously. Venesection was also done. Treatment to be successful must be started as soon as possible, and therefore it is of great importance that this complication of arsenical therapy be quickly recognized. In every case of sudden cerebral disaster in a young adult the question of previous arsenical treatment should be considered.

Discussion

This picture conforms to the usual type previously described in the literature—severe cerebral symptoms, with coma and epileptiform convulsions. The onset generally occurs after the second or third injection of an arsenobenzene preparation, and can happen as readily in the healthy subject as in the unfit. The main features in the present case are the haemorrhages, and extreme congestion of vessels of white matter coupled with blocking of cerebral capillaries and occasional rupture. There was no evidence of non-haemorrhagic perivascular areas of necrosis and demyelination as observed by Russell in her cases. This may have been due to the fact that this patient did not survive long enough for these findings to develop. Two of Russell's cases in which these changes were present survived for four days after onset of acute symptoms. The third of her patients died within six hours; evidence of necrosis and demyelination in the central nervous system was scanty.

The causal factor in arsenical encephalopathy is unknown, and seems to be unrelated to the arsenic radical, as poisoning by arsenic in an inorganic form does not give rise to such cerebral symptoms. It also seems unlikely that overdosage is at fault, as in most recorded cases symptoms have arisen shortly after the second or third injection. It is apparently not of the nature of a Herxheimer reaction, because cases are recorded (Glaser, Imerman, and Imerman, 1935) in which cerebral complications followed arsenical therapy in non-syphilitic subjects.

As symptoms occur most frequently after the second or third injection of an arsenical preparation it seems possible that the cerebral phenomena may be in the nature of an allergic reaction, although this does not seem to be of a permanent nature, as Lees mentions a case in which treatment with an arsenobenzene compound administered intramuscularly was resumed after recovery from haemorrhagic encephalitis without ill effects. There appears to be some relation between purpuric eruptions due to arsenobenzene preparations and haemorrhagic encephalitis (Winter, 1940). It may be that both are due to a toxic action of the benzene radical on capillaries. Organic arsenicals are well known as a cause of thrombocytopenic purpura, and it is possible that in some cases of haemorrhagic encephalopathy the toxic action is due to disintegration of arsenobenzene compounds in the blood, with resulting thrombocytopenia and capillary damage. The case described by Winter in which purpura was a feature could fit in with such a theory. I have been unable to find any reference in the literature to the platelet count in arsenical encephalitis.

The raised cerebrospinal-fluid protein in this case, with a normal cell content, is unusual, as was the increase in the C.S.F. pressure. In most cases described the protein has been

normal and the pressure also normal. In the present case, as in others described, the Wassermann reaction was positive in the blood but negative in the C.S.F.

In most cases previously recorded, cerebral complications of arsenobenzene therapy are referred to as haemorrhagic encephalitis. In view of the clinical picture and pathological findings, encephalopathy seems a more fitting description to apply to this complication.

Summary

A case of arsenical encephalopathy with pathological findings is described.

Attention is drawn to the need for early recognition of this condition, as treatment seems unavailing unless instituted in the first few hours after onset.

A short review of the literature is given. No adequate aetiology has been found to account for cerebral complications following arsenobenzene therapy.

I wish to thank Lieut.-Col. G. L. Montgomery, R.A.M.C., Assistant Director of Pathology, Scottish Command, for the post-mortem findings in this case, and Dr. A. A. F. Peel for advice and criticism; also the Department of Health for Scotland for permission to publish this report.

REFERENCES

- Friedman, C. F., and Shinefeld, M. A. (1941). *Amer. J. Syph. Gon. V.D.*, **35**, 610.
 Friedman, E. D., and Newman, E. (1941). *J. nerv. ment. Dis.*, **94**, 606.
 Glaser, M. A., Imerman, C. F., and Imerman, S. W. (1935). *Amer. J. med. Sci.*, **189**, 64.
 Lees, David (1937). *Diagnosis and Treatment of Venereal Diseases*, 3rd ed., Edinburgh.
 Russell, D. S. (1937). *J. Path. Bact.*, **45**, 357.
 Winter, H. G. (1940). *J. R.A.M.C.*, **74**, 161.

ETHYL CHLORIDE ANALGESIA

BY

J. D. ROCHFORD, M.B., D.A.

Captain, R.A.M.C.

AND

B. T. BROADBENT, L.D.S.

Captain, A.D. Corps

(From a General Hospital in the M.E.)

The term "analgesia" implies the loss of pain sense without the loss of consciousness or the sense of touch (Guedel, 1937). It is generally accepted that during induction of anaesthesia by inhalation a phase of analgesia is passed through (Guedel, 1937). This phase starts at the beginning of induction with a relative blunting of the sense of pain (relative analgesia), and passes to a complete state of analgesia (total analgesia). The analgesic phase ends with the loss of consciousness of the patient, some drugs giving a longer and better analgesic period than others. These drugs have been used for a variety of purposes: chloroform analgesia in obstetrics; trichlorethylene analgesia for the relief of pain in tic douloureux (Striker *et al.*, 1935) and more recently for painful dressings; nitrous oxide in combination with air or oxygen in midwifery and dental work (Minnitt, 1934).

- The limitation of the method is the difficulty of maintaining the analgesic state without slipping into the second and most dangerous stage of anaesthesia with its attendant risk of ventricular fibrillation. Lincoln (1941) has made an advance in the production of analgesia by using ethyl chloride in combination with nitrous oxide by the nasal route. It was considered that it might be of advantage to investigate the effects of ethyl chloride alone without using nitrous oxide. This we have done with success in 90 cases, the majority being dental extractions. All these patients were soldiers, many of whom are anaesthetic-resistant subjects.

The Method

The apparatus required is two tubes of ethyl chloride, a dental prop, some vaseline, and a roll of gauze. The lips are smeared with vaseline and a dental prop is inserted. An oblong of gauze, about 2 in. by 6 in., is crumpled and placed between the teeth, but not so far back as to cause gagging. The patient is asked to breathe to-and-fro through his mouth alone. He is told that the vapour will not put him to sleep but will